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QUALITY OF HEALTH CARE—HUMAN EXPERIMENTATION, 1973

HEARINGS

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON LABOR AND PUBLIC WELFARE UNITED STATES SENATE

NINETY-THIRD CONGRESS

FIRST SESSION

ON

S. 974

To amend the Public Health Service Act to provide, in the training of health professionals, for an increased emphasis on the ethical, social, legal, and moral implications of advances in biomedical research and technology

S. 878

To amend the Public Health Service Act to provide for restrictions on funds for experimental use

S.J. Res. 71

To provide for a study and evaluation of the ethical, social, and legal implications of advances in biomedical research and technology

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FEBRUARY 21 AND 22, 1973

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U.S. GOVERNMENT PRINTING OFFICE
93-999 O WASHINGTON : 1973

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CONTENTS

Text of: Page
S. 878 6
S. 974 11
S.J. Res. 71 50
S. 934 181

CHRONOLOGICAL LIST OF WITNESSES

WEDNESDAY, FEBRUARY 21, 1973

Edwards, Charles C., M.D., Commissioner of Food and Drugs, Department of Health, Education, and Welfare, accompanied by Henry E. Simmons, M.D., Director, Bureau of Drugs, Food and Drug Administration, DHEW; Peter Barton Hutt, Assistant General Counsel, Department of Health, Education, and Welfare; Gerald F. Meyer, Director, Office of Legislative Services, Food and Drug Administration, DHEW; John S. Zapp, D.D.S., Deputy Assistant Secretary for Legislation (Health), DHEW 12
Burgess, Anna, Monterey, Tenn.; Marcia Greenberger, Center for Law and Social Policy, Washington, D.C.; and Nathan Kase, M.D., Yale University School of Medicine, a panel 56
Kase, Nathan, M.D., chairman of Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Conn 60
Brooks, Leonard, M.D., New Woman's Clinic, Washington, D.C 78
Hutcheson, Robert, Jr., M.D., Tennessee Department of Health, Department of Family Planning, Memphis, Tenn 82
Brown, James S., M.D., superintendent, Arlington Hospital and School, Arlington, Tenn 94

THURSDAY, FEBRUARY 22, 1973

Wolfe, Dr. Sidney, and Anita Johnson, Health Research Group, Washington, D.C 194
Javits, Hon. Jacob K., a U.S. Senator from the State of New York 196
Greenwald, Peter, M.D., director, Cancer Control Bureau, New York State 212
Harrington, Donald, M.D., medical director, accompanied by Robert Talley, M.D., associate medical director, San Joaquin Foundation for Medical Care, Stockton, Calif 219
Goddard, James L., M.D., chairman of the board, Ormont Drug & Chemical Co., Englewood, N.J 260
Veatch, Robert, Ph. D., Hastings Institute, Hastings-on-Hudson, N.Y 265

STATEMENTS

Brooks, Leonard, M.D., New Woman's Clinic, Washington, D.C 78
Brown, James S., M.D., superintendent, Arlington Hospital and School, Arlington, Tenn 94
Burgess, Anna, Monterey, Tenn.; Marcia Greenberger, Center for Law and Social Policy, Washington, D.C.; and Nathan Kase, M.D., Yale University School of Medicine, a panel 56
Edwards, Charles C., M.D., Commissioner of Food and Drugs, Department of Health, Education, and Welfare, accompanied by Henry E. Simmons, M.D., Director, Bureau of Drugs, Food and Drug Administration, DHEW; Peter Barton Hutt, Assistant General Counsel, Department of Health, Education, and Welfare; Gerald F. Meyer, Director, Office of Legislative Services, Food and Drug Administration, DHEW; John S. Zapp, D.D.S., Deputy Assistant Secretary for Legislation (Health), DHEW 12
  Prepared statement 33
Goddard, James L., M.D., chairman of the board, Ormont Drug & Chemical Co., Englewood, N.J 260

Page
Greenwald, Peter, M.D., director, Cancer Control Bureau, New York State 212
Harrington, Donald, M.D., medical director, accompanied by Robert Talley, M.D., associate medical director, San Joaquin Foundation for Medical Care, Stockton, Calif 219
Hutcheson, Robert, Jr., M.D., Tennessee Department of Health, Department of Family Planning, Memphis, Tenn 82
Javits, Hon. Jacob K., a U.S. Senator from the State of New York 3, 196
Kase, Nathan, M.D., chairman of Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Conn 60
Veatch, Robert, Ph. D., Hastings Institute, Hastings-on-Hudson, N.Y 265
Wolfe, Sidney M., M.D., Health Research Group, Washington, D.C 191

ADDITIONAL INFORMATION

Articles, publications, etc.:
  "Adverse Reactions and Drug Interaction—A Critical Analysis of the Talley Paper," released February 20, 1973 277
  Arlington Hospital and School, form letter from, to parents of student nurses, signed by Edward N. Morgan, M.D., director of clinical services 96
  Consent form of State family planning clinics 108
  "Covert Drug Abuse Among Voluntary Hospitalized Psychiatric Patients," by Arnold G. Blumberg, Melvin Cohen, Ph. D., Andre M. Heaton, and Donald F. Klein, M.D., from the Journal of the American Medical Association, September 20, 1971 316
  Depo-Provera:
    Effects and side effects 110
    Program, permit for, from Arlington Hospital and School, Arlington, Tenn 73
    Program, report on, from Arlington Hospital and School, Arlington, Tenn 110
    Written informed consent form for contraceptive studies, revised 70
  "Diethylstilbestrol Contraindicated in Pregnancy," from the FDA Drug Bulletin, November 1971 188
  "Drug Establishment," by James L. Goddard, from Esquire, March 1969 319
  "Drug Utilization and Peer Review in San Joaquin," by Robert B. Talley, M.D., F.A.C.P., and Marc F. Laventurier, B.S., Pharm., F.A.C.A 223
  Injection contraceptive consent form 108
  Legal status of approved labeling for prescription drugs; prescribing for uses unapproved in the Food and Drug Administration (from the Federal Register, August 15, 1972) 15
  "Morning-after Pill":
    Article, by Kathleen Weiss, Advocates for Medical Information, Ann Arbor, Mich., November 15, 1972 310
    Report on, by Health Research Group 201
Communications to:
  Fleming, Robben, president, University of Michigan, Ann Arbor, Mich., from Anita Johnson and Sidney M. Wolfe, M.D., Health Research Group, Washington, D.C., December 8, 1972 (with enclosure) 314
  Goldberg, Dr. Delphis C., Intergovernmental Relations Subcommittee, House Committee on Government Operations, House of Representatives, from Gerald F. Meyer, Office of Legislative Services, October 12 (with enclosures) 115
  Kennedy, Hon. Edward M., a U.S. Senator from the State of Massachusetts, from:
    Humphrey, Hon. Hubert, a U.S. Senator from the State of Minnesota, Committee on Agriculture and Forestry, March 5, 1973 with enclosure 177
    Hutcheson, Robert H., Jr., M.D., assistant commisisoner, Department of Public Health, State of Tennessee, Nashville, Tenn., February 22, 1973 88
Memorandum to:
  Executive directors, medical directors, chairmen, medical advisory committees, from National Medical Department of Planned Parenthood-World Population, New York, N.Y., November 1971 214

QUALITY OF HEALTH CARE—HUMAN EXPERIMENTATION, 1973

WEDNESDAY, FEBRUARY 21, 1973

U.S. Senate,
Subcommittee on Health of the
Committee on Labor and Public Welfare,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m. in room 4232, Dirksen Building, Senator Edward M. Kennedy, subcommittee chairman, presiding.

Present: Senators Kennedy, Nelson, Schweiker, and Taft.

Staff members present: LeRoy G. Goldman, professional staff member; and Jay B. Cutler, minority counsel.

Senator Kennedy. The subcommittee will come to order.

Today, as we begin this important set of oversight hearings on biomedical research and human experimentation, scientists may stand on the threshold of being able to recreate man. They will soon have the power to modify and control his behavior—indeed they can already do so in certain controlled, clinical settings.

In the last decade, we have witnessed an unparalleled expansion of our technological capabilities. The technology of biomedical research is the technology of man. Today, we have more biomedical research scientists at work on more kinds of projects than at any time in our history. Their success in these endeavors has taken us beyond the frontiers of man's understanding. And the gap between the development of the technology of man, and our capacity to understand the nature and implications of that technology, widens every day.

In the last decade, we have seen a surgeon hold a human heart in his hands and transplant it into another person's body; we have seen scores of surgeons renew life for thousands of people by the transplantation of kidneys; we have seen scientists unravelling the mysteries of the genetic code, learning how to alter the very structure of the building blocks of life; we have seen scientists begin to unlock the mysteries of the brain and begin to understand the physical basis of feelings—of sorrow and joy, of pain and pleasure, of anger and understanding; we have seen a breakthrough in the treatment of Hodgkins disease, a dreaded cancer of the lymph nodes; we have seen a vaccine developed to eliminate measles. We have all been touched by, and have all profited by, the fruits of biomedical research.

In the next decades scientists will place even more powerful tools in our hands. We will, as a society, have to be ready to answer many questions:

Under what conditions, if any, would genetic manipulation of our population be allowed?

Under what conditions, if any, would neurosurgical or pharmacologic modifications of behavior be allowed?

What constitutes death?

Who will have access to lifesaving equipment if it is in short supply—like kidney dialysis machines, or artifical hearts?

When may a society expose some of its members to harm in order to seek benefits for the rest of its people?

This set of hearings will explore many of these questions. We will hear from those who believe these new and powerful tools will help us realize our full potential as a nation and as a people; we will hear from others who feel that our basic and most cherished freedoms are threatened by the technology of man.

On Friday, we will explore the status of research into the nature of the human mind. We will consider the implications of psychosurgery and electrical stimulation of the brain; we will be updated by Dr. B. F. Skinner, on his behavioral research. On March 6 we will look at prisoners as subjects of biomedical research and ask what special ethical and moral considerations come into play when research is carried out on a captive population. On March 7, we will glimpse into the future of genetics and human engineering; we will look into the future of surgery; and we will look to the past accomplishments of biomedical research. On March 8 we will try to get answers to some of the questions raised and will try to formulate more appropriate questions. We will inquire as to the next steps our society must take in order to master the technology of man, so that we may come to understand it, guide its application and not become its victims. If we find that legislation is required, we will move promptly to enact it.

It is our hope that these hearings will encourage continued support of and advancement of, biomedical research. It is also our hope that they will encourage a closer look at the ethical and moral implications of what we have already done and will soon be able to do.

It is in the daily practice of medicine that the products of biomedical research eventually find their application. The first two days of these hearings will demonstrate that for a variety of reasons, the medical care system is structured so that those products are easily misused. The result is that human experimentation is part of the routine practice of medicine.

The rapid development of new knowledge has placed a heavy burden on the practicing physician. Scientific journals proliferate each year, and it is becoming harder for the physician to keep up—to know what the new drugs, new techniques, and new treatments are. Yet each physician wants to know and be able to use the new knowledge for the benefit of his patients.

This sometimes results in the use of new techniques and new treatments that are only imperfectly understood. Sometimes, they are not yet even officially sanctioned. The absence of sufficient quantity control mechanisms in the practice of medicine, coupled with the almost unlimited freedom of action which physicians have in the treatment of their patients, encourages the development of patterns of medical practice that may well be premature and based on an inadequate understanding of the new technique or new drug.

These hearings will describe the premature development of practice patterns with respect to two drugs—DepoProvera and DES. Both of these drugs have certain approved uses and both are considered to be experimental for other uses.

When a new drug is developed or when a new use is proposed for an old drug, the Food and Drug Administration supervises well regulated tests to determine if the new use is safe and effective. During this experimental test period the drug is not officially approved by the FDA for common use. We will demonstrate that although DepoProvera and DES are officially classified as experimental for use as birth control agencies, both are in widespread use in this country, without informed consent or proper medical followup. When a physician prescribes a drug for a purpose other than that for which it has been approved, he is performing an experiment. And in the absence of sufficient quality control mechanisms, his latitude to perform such experiments is nearly unlimited.

There is no malice involved in such a situation. In fact, the reverse is probably true—the physician may have independently come to the conclusion that the drug is good and safe, and that the FDA is too slow in approving it. He may not know that the drug is experimental. He may simply be playing a hunch based on years of clinical experience. The question is whether or not we can tolerate a system where the individual physician is the sole determinant of the safety of an experimental procedure.

After all, it is the patients who must live with the consequences of that decision.

Our first witness is Dr. Charles Edwards, Commissioner of the Food and Drug Administration. In 1962 Dr. Edwards became associate director of medical education of the American Medical Association and in 1963 was named director of AMA's division of socio-economics activity. He became Commissioner of the Food and Drug Administration in 1969.

We welcome him back to this committee, and we are expecting big things from him in the future, but first Senator Javits' opening statement will be printed at this point.

OPENING STATEMENT OF HON. JACOB K. JAVITS, A U.S. SENATOR FROM THE STATE OF NEW YORK AND RANKING MINORITY MEMBER OF THE SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE

Senator JAVITS. As the Health Subcommittee of the Committee on Labor and Public Welfare (of which I am ranking minority member) begins hearings on such issues as psychosurgery, organ transplants, genetic manipulations, sterilization procedures for criminal behavior, brain-washing, mind control and mind expanding techniques, and yes, even the very concept of birth and death itself, the urgent need to adequately protect the rights and welfare of human subjects in all research activities becomes imperative.

To assure meaningful legal controls of all federally supported research activities involving human subjects, I have introduced the "Protection of Human Subjects" bill S. 878, and ask that the full text of the bill be printed in the hearing record at the conclusion of my remarks.

The bill is patterned upon NIH research guidelines and outlines flexible operating procedures which can be adapted to a variety of federally funded grant an contract mechanisms to safeguard the rights and welfare of human subjects.

There is no doubt but that we must constantly and continually encourage research into the great enigma of man and his world if we are to eventually overcome the abysmal depths of ignorance and disease.

But we must guard against self delusion lest it harm that precious quality of life which is so uniquely human—also to be humane. Scientific inquiry must constantly be blended with judgment, compassion and sympathy, the true synthesis of humaneness and humanity.

The dilemma of what reforms would be imposed upon scientific inquiry and medical experimentation will require the leadership of the medical profession. The recent book, *Research on Human Subjects—Problems of Social Control In Medical Experimentation*, by Bernard Barber, John J. Lally, Julia Loughlin Makarushka, and Daniel Sullivan, unfortunately concludes that medical schools ". . . have not been ethical leaders with regard to peer group review. They have a proud record of scientific leadership, but their record in ethical innovation is not distinguished."

Medical schools have primary responsibility for the education and training of those who will carry on the medical profession as practitioners, as researchers, and as teachers, and are the natural environment to become ethical leaders in respect to efforts to safeguard the rights and welfare of the human subjects of biomedical research.

I believe that unless significant improvement is made in the curricula of our medical schools—to provide ethical leadership in protecting and safeguarding the rights of human subjects—it will augur ill for our nation's future. Therefore, I am introducing with Senator Williams, Chairman of the Committee, a bill to authorize special project grants to medical schools to stimulate the development of programs in the ethical, social and legal implications of the advances in biomedical science and technology, with emphasis upon their implications for individuals and society. I request that the full text of the bill also be printed in the hearing record at the conclusion of my remarks.

It is imperative that we maintain a constant vigil lest the zeal which first motivated and then impelled man forward in his never-ending quest for enlightenment be like the sorcerer's apprentice, exceeding its bounds and unfettered, cause us to outdistance our own capacity for the best values of humanity; and this could easily result in moral suicide.

At the same time, excessive rigidity in the regulation of human subject experimentation because of some improprieties in ethical self regulation would, I believe, be to the disadvantage of the individual and society. Civilized society cannot tolerate the callous diregard of human rights for any purpose and mankind would be badly served if we write rigid laws to govern research practices and scientific investigation, but research, development and the reduction to practice of new ideas are not carried out in a practical, ethical, or legal vacuum and the public interest would not be served by such an inflexible approach.

In view of my own deep personal concern about this subject, I have sponsored—with the Chairman of the Labor and Public Welfare Committee, Senator Williams; the ranking minority member of the Health Subcommittee, Senator Schweiker; and the Chairman of the Health Subcommittee, Senator Kennedy—a special Congressional briefing session on February 27 about the advances in biomedical science and their important consequences for the future of mankind generally, and for our country in particular. These new developments have profound ethical and legislative implications, and so require understanding on our part as legislators if they are to be used for maximum benefit to our people.

[The texts of S. 878 and S. 974 follow:]

93d CONGRESS
1st Session

S. 878

IN THE SENATE OF THE UNITED STATES

February 15, 1973

Mr. Javits introduced the following bill; which was read twice and referred to the Committee on Labor and Public Welfare

---

A BILL

To amend the Public Health Service Act to provide for restrictions on funds for experimental use.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That part A of title III of the Public Health Service Act is amended by inserting at the end thereof the following new section:

"PROTECTION OF HUMAN SUBJECTS

"Sec. 310C. (a) Notwithstanding any other provision of law, unless enacted after the enactment of this Act expressly in limitation of the provisions of this section, funds appropriated for any fiscal year to carry out any Federal program shall not be made available to any organization unless such organization has given acceptable assurance that none of these funds will be used in support of an activity involving human subjects at risk in programs of research, development, or demonstration in the absence of initial and continuing review and approval by an appropriate organizational committee. This review shall determine that the rights and welfare of the subjects involved are adequately protected, that the risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent is to be obtained by methods that are adequate.

"(b) The organizational committee must be composed of sufficient members with such varying backgrounds of competence as to assure complete and adequate review. No member of such committee shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the committee.

"(c) For the purposes of this section only, the term 'informed consent' shall mean the consent of a person, or his legal representative, so situated as to be able to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress, or other form of constraint or coercion. The information to be given to the subject shall include the following basic elements in all but exceptional cases:

"(1) a fair explanation of the procedures to be followed, including an identification of any which are experimental;

"(2) a description of any attendant discomforts and risks reasonably to be expected;

"(3) a description of any benefits reasonably to be expected;

"(4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

"(5) an offer to answer any inquiries concerning the procedures; and

"(6) an instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.

In addition, the agreement, written or oral, entered into by the human subject or from the human subject's legal representative, shall include no exculpatory language through which the subject is made to waive, or to appear to waive, any of his legal rights, or to release the institution or its agents from liability for negligence. Any organization which initiates, directs, or engages in programs of research, development, or demonstration which require informed consent shall keep a permanent record of such consent and the information provided the subject and develop appropriate documentation and reporting procedures as an essential administrative function.

"(d) For the purposes of this section only the term 'organization' means any Federal, State, municipal, or other Government agency, or any corporation, institution, agency, or other legally accountable person.

"(e) The term 'human subject at risk' means an individual who may be exposed to the possibility of harm—physical, psychological, sociological, or other—as a consequence of any activity which goes beyond the application of those established and accepted methods necessary to meet the individual's needs.

"(f) Nothing in this section shall prevent Federal program staff from establishing and maintaining internal review procedures to identify risks to subjects in Federal programs, and from making independent determinations that the rights and welfare of the subjects involved are adequately protected, that the risks to an individual are balanced by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent is to be obtained by methods that are adequate and appropriate.

"(g) 'Exceptional cases', as used in paragraph (c) of this section, which exceptions are to be strictly applied, are cases where it is not feasible to obtain the subject's consent or the consent of his representative, or where, as a matter of professional judgment exercised in the best interest of a particular subject under care, it would be contrary to that subject's welfare to obtain his consent as the communication of information to obtain consent would seriously affect the subject's' disease status and the physician has exercised a professional judgment that under the particular circumstances of this subject's case, the subject's best interests would suffer if consent were sought.

"(h) The Secretary of Health, Education, and Welfare shall from time to time, and in cooperation with other departments and agencies of the Federal Government, identify those Federal programs which may involve human subjects at risk, determine the form the assurances required by this section shall take, set guidelines for the establishment of operation of organizational committees, and establish such additional regulation as the implementation of this section may require.".

93D CONGRESS
1ST SESSION

S. 974

IN THE SENATE OF THE UNITED STATES

FEBRUARY 22, 1973

Mr. JAVITS (for himself, Mr. WILLIAMS, and Mr. MONDALE) introduced the following bill; which was read twice and referred to the Committee on Labor and Public Welfare

---

A BILL

To amend the Public Health Service Act to provide, in the training of health professionals, for an increased emphasis on the ethical, social, legal, and moral implications of advances in biomedical research and technology.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That section 772 (a) (7) of the Public Health Service Act (42 U.S.C. 201 et seq.) is amended by inserting immediately before the semicolon at the end thereof the following: ", or (C) providing increased emphasis on, the ethical, social, legal, and moral implications of advances in biomedical research and technology with respect to the effects of such advances on individuals and society".

STATEMENT OF CHARLES C. EDWARDS, M.D., COMMISSIONER OF FOOD AND DRUGS, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, ACCOMPANIED BY HENRY E. SIMMONS, M.D., DIRECTOR, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION, DHEW; PETER BARTON HUTT, ASSISTANT GENERAL COUNSEL, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; GERALD F. MEYER, DIRECTOR, OFFICE OF LEGISLATIVE SERVICES, FOOD AND DRUG ADMINISTRATION, DHEW; JOHN S. ZAPP, D.D.S., DEPUTY ASSISTANT SECRETARY FOR LEGISLATION (HEALTH), DHEW

Dr. EDWARDS. Thank you, Mr. Chairman. I would like first to take the opportunity to introduce my colleagues.

On my immediate right is Dr. John Zapp, Deputy Assistant Secretary for Legislation on Health, Department of Health, Education, and Welfare. To his right is Dr. Henry E. Simmons, Director, Bureau of Drugs, Food and Drug Administration. On my left is Mr. Peter Hutt, Assistant General Counsel, and on his left is Mr. Gerald Meyer, who is Director of Food and Drug Administration Legislative Department.

We are pleased to appear before you today——

Senator KENNEDY. You have a very extensive statement here. We would be glad to include it in its entirety in the record. You can proceed whichever way you like. We have a lot of questions we would like to ask you.

Dr. EDWARDS. Mr. Chairman, I would like to have it all included, with your permission, in the record. We have cut it down rather extensively.

Senator KENNEDY. Your prepared statement in its entirety will appear at the end of your testimony.

Dr. EDWARDS. With your permission, I will go ahead with the way we have cut it down.

As I said, we are pleased to appear before you today to discuss the policies and programs of the Food and Drug Administration with regard to the safeguards provided for humans participating in clinical drug trials leading to the development of new drugs.

It should be understood at the outset that this is a difficult and complex subject with serious scientific, moral, and ethical considerations.

Perhaps the most critical point that can be emphasized this morning is the real dilemma that exists with regard to any research or investigational study. At the present time, there is no species of animal or "in vitro" laboratory test system that can be relied on alone to be completely predictive of what to expect in man. In other words, no matter how much animal or laboratory data we can collect, at some point we must address ourselves to the question, "What does this data mean for man and how will a human be affected by this drug?" This is why clinical studies are necessary. If we should ever decide that clinical studies cannot be undertaken, then we effectively terminate further drug development and progress in medicine. Until we have an animal or laboratory system that is perfectly predictive for man, we are and will be dependent on adequate and well-controlled clinical research.

Studies in children. In this general context one should discuss the use of investigational drugs or other new therapeutic approaches in children. There is, understandably, a natural reluctance on the part of some scientists to conduct studies in children. But the fact is that when children are sick, they too may need drugs and it would surely be unethical to administer to children drugs which have not been studied in children. Infants and children often do not metabolize drugs as adults do. Moreover, it is usually not possible to predict the correct dose of a drug for a child merely by regarding it as a miniature adult and lowering the dose proportionately.

Experts in pediatrics and in pharmacology have concluded that drugs must be studied in children before they are used in children; in fact, FDA requires that drugs be studied in all age groups for which a drug is intended.

Clearly when a drug or other therapeutic approach is studied in children, the children should be expected to benefit from the course of treatment being studied. Other studies on the effects of the drug may also be done simultaneously and recorded, but a benefit to the patient should exist to justify the study. The FDA has such a working policy on the use of investigational drugs in children and is working with experts of the American Academy of Pediatrics to develop guidelines for drug testing in children.

The 1962 Drug Amendments to the Federal Food, Drug, and Cosmetic Act required FDA to exercise strict control over the use of investigational drugs undergoing clinical trials. The IND procedure offers comprehensive control of the developmental testing of drugs in this country and insures that the proposed studies are justifiable and do not expose human beings to undue risks. Our regulatory process also requires that the studies be well controlled and therefore meaningful.

Among other things, the 1962 Drug Amendments specifically required that consent be obtained except when not feasible or when, in the judgment of the investigator, it is contrary to the best interests of the patient. In 1967, FDA clarified and strengthened this statutory provision by regulations requiring written consent in the first two phases of human clinical trials and a documentation if oral consent is obtained in place of written consent in Phase III.

FDA's action in 1970 further reduced the possibility of patients being exposed to unwarranted risk. A new regulation provided for a 30-day delay before clinical studies could be initiated in order to allow for a preliminary screen of the proposed study to assure that the drug has been adequately studied in laboratory animals and would be studied under a scientifically sound protocol that would not expose human subjects to an unwarranted risk.

Also pursuant to the 1962 Drug Amendments, the FDA has acted to "disqualify" clinicians because of improper and unethical practices. A program of surveillance of clinical investigations began in 1967, and specific formal procedures for such "disqualifications" of clinical investigators were established in 1968. Since then, sixteen investigators have been disqualified and 20 have been reprimanded.

Senator KENNEDY. What are the types of things they are disqualified for?

Dr. Edwards. I think, Mr. Chairman, primarily because of erroneous data, data that cannot be confirmed by proper clinical trials and proper testing. Dr. Simmons, would you want to add to that?

Dr. Simmons. Not following the protocol agreed on, Mr. Chairman.

Dr. Edwards. In other words, erroneous data that is being submitted to the Food and Drug Administration is probably the most frequent.

When an investigator is disqualified, he is ineligible to receive investigational drugs and all the sponsors employing the individual as an investigator and appropriate government agencies are notified of this disqualification. The data generated by a disqualified investigator cannot, of course, be utilized by the manufacturer in support of his application for marketing approval. In the case of reprimands, sponsors are routinely notified of investigators' shortcomings since these are usually indicative of poor monitoring by the sponsor. It should be noted that criminal cases have been filed for fraudulent data submitted and one such case has recently been referred to the Department of Justice and is now under their review.

Good investigational practices are, of course, intimately related to good monitoring by the sponsors of the study. For the coming year, FDA has designed a program to permit a more precise determination of the quality of such monitoring in this country. Some 8–12 studies on new significant compounds have been selected for intensive surveillance. This is an initial step to improve the existing approach of primarily investigating researchers under suspicion of violation. The increased coverage provided by this program should give a truer picture of the state of affairs of clinical investigations carried out under investigational new drug regulations in this country.

FDA's regulatory procedures have also been strengthened by providing for local review of studies to determine whether proposed studies are justified in a particular area and to provide a local system of assurance that the study is conducted ethically and in compliance with the law. In 1971, FDA promulgated regulations to require institutional committee review of investigational new drug studies. If such studies are conducted on institutionalized subjects or by an individual affiliated with an institution assuming responsibility, assurances must be provided that an institutional review committee is responsible for initial and continuing review of the study. A review committee must be composed of persons of varying backgrounds—lawyers, clergy, laymen, as well as scientists—and cannot be composed solely of physicians. An intramural FDA committee now provides this type of review for all studies involving human subjects which are conducted by FDA.

In other efforts to further examine the many issues raised regarding drug testing on human subjects, a contract was awarded to the Drug Research Board of the NAS–NRC to help define the relative roles of the sponsor and the Food and Drug Administration with regard to clinical investigations. FDA is now in the process of reviewing the report from the NRC Drug Research Board to determine what modifications can be made in the current system to improve it further so that investigators are aware of their responsibilities, that research facilities are adequate, that patient followup is appropriate and that consent is informed and obviously voluntary.

Your staff have expressed particular interest in regards to procedures for the approval of additional uses or indications for drugs already on the market. Studies of new uses of a drug are also subject to our IND controls. Adequate and well-controlled studies are required to establish the safety and effectiveness of the drug for that particular use. It is illegal to promote and market or ship a drug in interstate commerce for an unapproved use without an IND.

However, the prescribing of an approved drug for an unapproved use by individual physicians in the practice of medicine is beyond the jurisdiction of the FDA.

A proposed regulation issued by FDA August 15, 1972, clearly outlined this issue and I would, at this time, like to offer that regulation for the record.

[The information subsequently supplied follows:]

[From the Federal Register, Aug. 15, 1972]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[21 CFR Part 130]

LEGAL STATUS OF APPROVED LABELING FOR PRESCRIPTION DRUGS; PRESCRIBING FOR USES UNAPPROVED BY THE FOOD AND DRUG ADMINISTRATION

Notice of proposed rule making

The widespread use of certain prescription drugs for conditions not named in the official labeling has led to questions concerning the legal responsibilities of the prescribing physicians, and the position of the Food and Drug Administration with respect to such use. Accordingly, the Commissioner proposes to add a new regulation clarifying the applicable legal requirements and specifying actions that may be taken by the Food and Drug Administration with respect to unapproved uses of approved prescription drugs.

Section 505 of the Federal Food, Drug, and Cosmetic Act prohibits the introduction or delivery for introduction into interstate commerce of any new drug without the filing of an investigational new drug plan or approval of a new drug application. Unlike the adulteration and misbranding provisions of the Act, the new drug provisions apply only at the moment of shipment in interstate commerce and not to action taken subsequent to shipment in interstate commerce. In United States v. Phelps Dodge Mercantile Co., 157 F. 2d 453 (9th Cir. 1946), cert. denied, 330 U.S. 818 (1947), the court held that violations while products are held for sale after interstate shipment did not come within the jurisdiction of the Act. As a result of that decision, Congress enacted the Miller amendment of 1948, 62 Stat. 582, amending section 301(k) of the Act to extend the reach of the adulteration and misbranding provisions of the Act to violations after interstate shipment. The 1948 amendment did not, however, also extend the reach of the new drug provisions of the Act, which are separate from the adulteration and misbranding provisions, to action taken after interstate shipment.

The major objective of the drug provisions of the Federal Food, Drug, and Cosmetic Act is to assure that drugs will be safe and effective for use under the conditions of use prescribed, recommended, or suggested in the labeling thereof. Thus, new drug approval and autibiotic drug certification are regulated by law, both in the prescriber's and the patient's interest. When a new drug is approved for marketing, the conditions of use that have been approved are required to be set forth in detail in the official labeling. This labeling must accompany the drug in interstate shipment and must contain adequate information for safe and effective use of the drug, including: Indications, effects, dosages, routes, methods, and frequency and duration of administration, contraindications, side effects, and precautions. The labeling is derived from the data submitted with the new drug application. It presents a full disclosure summarization of drug use information, which the supplier of the drug is required to develop from accumulated clinical experience, and systematic drug trials consisting of preclinical investigations and adequate well-controlled clinical investigations that demonstrate the drug's safety and the effectiveness it purports or is represented to possess.

If an approved new drug, is shipped in interstate commerce with the approved package insert, and neither the shipper nor the recipient intends that it be used for an unapproved purpose, the requirements of section 505 of the Act are satisfied. Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.

This interpretation of the Act is consistent with congressional intent as indicated in the legislative history of the 1938 Act and the drug amendments of 1962. Throughout the debate leading to enactment, there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient. Congress recognized a patient's right to seek civil damages in the courts if there should be evidence of malpractice, and declined to provide any legislative restrictions upon the medical profession.

In the 1938 Act and the 1962 amendments, however, Congress clearly required the Food and Drug Administration to control the availability of drugs for prescribing by physicians. Under the 1938 Act, a new drug could not be marketed unless a new drug application establishing the drug's safety had been allowed to become effective by the Food and Drug Administration. Under the 1962 amendments, no new drug is permitted on the market until the Food and Drug Administration approves a new drug application demonstrating both its safety and effectiveness.

Under the 1962 amendments, moreover, the Food and Drug Administration is required to review the labeling for every new drug, including the package insert for prescription new drugs, and to approve it as not false or misleading in any particular. In approving the labeling the Food and Drug Administration must determine both that the content is entirely truthful, and that it omits no information pertinent to the safe and effective prescribing of the drug by the physician. Congress intended the labeling to be a full, complete, honest, and accurate appraisal of the important facts that have reliably been proved about the drug.

Thus, although it is clear that Congress did not intend the Food and Drug Administration to regulate or interfere with the practice of medicine, it is equally clear that it did intend that the Food and Drug Administration determine those drugs for which there exists substantial evidence of safety and effectiveness and thus will be available for prescribing by the medical profession, and additionally, what information about the drugs constitutes truthful, accurate, and full disclosure to permit safe and effective prescription by the physician. As the law now stands, therefore, the Food and Drug Administration is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.

Although the Act does not require a physician to file an investigational new drug plan before prescribing an approved drug for unapproved uses, or to submit to the Food and Drug Administration data concerning the therapeutic results and the adverse reactions obtained, it is sometimes in the best interests of the physician and the public that this be done. The physician should recognize that such use is investigational, and he should take account of the scientific principles, including the moral and ethical considerations, applicable to the safe use of investigational drugs in human patients. When the results of treatment are reported completely and accurately the data may be helpful to patients and physicians as well as to the Food and Drug Administration. Such information can lead to warnings against dangerous unapproved uses, or, on the other hand, to acceptance of previously unknown uses.

Physicians have been concerned that the failure to follow the labeling of a drug may render them unduly liable for malpractice.

Although labeling, along with medical articles, tests, and expert opinion, may constitute evidence of the proper practice of medicine, it is not controlling on this issue. The labeling is not intended either to preclude the physician from using his best judgment in the interest of the patient, or to impose liability if he does not follow the package insert. A physician should recognize, however, that the package insert represents a summary of the important information on the conditions under which the drug has been shown to be safe and effective by adequate scientific data submitted to the Food and Drug Administration.

Where the unapproved use of an approved new drug becomes widespread or endangers the public health, the Food and Drug Administration is obligated to investigate it thoroughly and to take whatever action is warranted to protect the public. Several alternative courses of action are available to the Food and Drug Administration under these circumstances, depending upon the specific facts of each case. These actions include: Requiring a change in the labeling to warn against or to approve the unapproved use, seeking substantial evidence to substantiate the use, restricting the channel of distribution, and even withdrawing approval of the drug and removing it from the market in extreme cases. When necessary, the Food and Drug Administration will not hesitate to take whatever action of this nature may be required to bring possible harmful use of an approved drug under control.

Section 1.106 of the regulations (21 CFR 1.106) requires the labeling to contain appropriate information with respect to all intended uses of the drugs. Thus, where a manufacturer or his representative, or any person in the chain of distribution, does anything that directly or indirectly suggests to the physician or to the patient that an approved drug may properly be used for unapproved uses for which it is neither labeled nor advertised, that action constitutes a direct violation of the Act and is punishable accordingly.

The Commissioner believes it important that the public, the medical profession, and the pharmaceutical industry fully appreciate the statutory provisions enacted by Congress that are controlling under these circumstances.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 701, 76 Stat. 781–785, as amended, 52 Stat. 1055–1056; 21 U.S.C. 355, 371) and under authority delegated to the Commissioner (221 CFR 2.120), it is proposed that the following new section be added to Part 130:

§ 130. Legal status of labeling, including package inserts and product brochures, for prescription drugs; prescribing for uses unapproved by the Food and Drug Administration

(a) The Food and Drug Administration approves labeling for a prescription new drug as part of the new drug approval process. Supplemental new drug applications may periodically result in revision of the labeling.

(1) The labeling approved by the Food and Drug Administration in a prescription new drug application summarizes all information with respect to the conditions of use for which substantial evidence is available to the Food and Drug Administration that the drug is safe and effective.

(2) A prescription new drug may not be shipped in interstate commerce when intended for uses not contained in the currently approved labeling. Such unapproved uses may include, inter alia, a different dosage, or a different patient population, or a different regimen, than that approved. Section 505 of the Federal Food, Drug, and Cosmetic Act requires that a manufacturer, physician, or other person who ships or requests shipment of a prescription new drug in interstate commerce with the intent, or for the purpose, of an unapproved use must first file with the Food and Drug Administration an investigational new drug plan as set out in § 130.3.

(3) Once a prescription new drug has been shipped in interstate commerce intended for its approved use(s) under approved labeling, the Federal Food, Drug, and Cosmetic Act does not require a physician to file with the Food and Drug Administration an investigational new drug plan in order to lawfully prescribe the drug for an unapproved use, when such prescribing is done as part of the practice of medicine.

(b) When an unapproved use of a new drug may endanger patients or create a public health hazard, or provide a benefit to patients or to the public health, the Food and Drug Administration is obligated to take one or more of the following courses of action:

(1) Revision of the package insert may be required to add a specific contraindication or warning against the unapproved use.

(2) The manufacturer may be required to obtain and submit the available data with respect to the unapproved use, or to sponsor clinical trials to determine the safety and effectiveness of the drug for the unapproved use.

(3) If substantial evidence of safety and effectiveness is available, revision of the package insert may be permitted or required to add the unapproved use as an approved use and to state the conditions under which the drug is safe and effective for that use.

(4) Revision of the package insert may be required to state that a prescription for the drug should not be refilled.

(5) Revision of the package insert may be required to state that the drug should be distributed only through specified channels (e.g., hospital pharmacies) and/or should be prescribed dispensed, or administered only by physicians with specified qualifications.

(6) The investigational new drug authority, as well as the new drug approval authority, may be invoked to impose a requirement that the drug may be distributed only through specified channels and/or may be prescribed, dispensed, or administered only by physicians with specified qualifications.

(7) The package of the drug dispensed to the patient may be required to contain a package insert containing appropriate information for the safe and effective use of the drug by the layman.

(8) The approval of the new drug application may be revoked.

Interested persons may, within 60 days after publication hereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 30, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc. 72-12812 Filed 8-14-72; 8:45 am]

Dr. EDWARDS. If an approved new drug is shipped in interstate commerce with the approved labeling and neither the manufacturer nor the recipient intends that it be used for an unapproved purpose, the requirements of the Act are satisfied. Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the labeling, without informing or obtaining the approval of the FDA.

This interpretation of the Act is required in light of the legislative history of the Act which is replete with statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the law did not purport to regulate the practice of medicine as between the physician and the patient.

Senator KENNEDY. If the Food and Drug Administration is not prepared to do this, who is?

Dr. EDWARDS. I think, Mr. Chairman, at least in my judgment, it is a combination of parties that should be involved in this.

I have outlined more or less our responsibility in being sure that there is adequate labeling. But once we have provided the adequate labeling, then I think it has to be a combination of adequate education of physicians, and I think it has to be adequate peer review—there has to be peer review organizations established that will give this kind of supervision and provide this kind of oversight.

I think these are the kinds of things that have to be encouraged by all of those that are involved.

Senator KENNEDY. You have been head of the Food and Drug Administration now for a number of years. At the present time, what is your impression about the effectiveness of peer review in this area?

Dr. EDWARDS. Well, I think that the whole subject of drug education and peer review needs to be strengthened. I do not think there is any question about that.

I think for too long the medical profession has relied too heavily on pharmaceutical industry for drug education. I think we should be playing a much more important role than we have in the past, and we are moving in that direction.

We have established a drug bulletin that goes out usually monthly to all the practicing physicians. But in addition to that, I think such things as the professional standards review organizations that are being considered by the administration and by the Congress are important new steps that need to be taken. I think some of the review establishments that have been set up in hospitals heretofore have not been particularly effective, and certainly much more needs to be done.

Senator KENNEDY. What you are saying is that under your legislative mandate, you are quite restricted. As I understand it, once you make a determination about a certain drug and approve it for experimental use, you have very little control over the actual practice of medicine or the way drugs are used by the individual doctor. As a matter of fact, you have a rather clear mandate from the Congress not to become involved in reviewing how drugs are actually going to be used.

Dr. EDWARDS. That is absolutely correct.

Senator KENNEDY. What you are really suggesting is that it is left to the medical profession itself to determine how physicians are going to use those drugs, and I suppose the question from a consumer's point of view is how he is to know whether the drug prescribed for him was really approved by the Food and Drug Administration for that purpose.

Dr. EDWARDS. Well, I think, of course, primarily the patients in this country have to rely upon their doctors being ethical and being reasonably well educated.

I think though this obviously is not enough, and we have to move more and more in the direction of having the peer review type of process established.

I certainly do not feel that the Food and Drug Administration as a regulatory agency should be regulating the practice of medicine. I think it has to be outside of our jurisdiction.

Senator KENNEDY. But you might very well run into the following situation: an individual doctor might think it a good idea to prescribe a certain drug for a certain need, but the best clinical researchers might have reservations about it. There is nothing the Food and Drug Administration is doing now that will stop a doctor from allowing his judgment to prevail over that of our best clinical researchers—is that not so?

Dr. EDWARDS. No, there is not. Again I think another responsibility of ours that we have not adequately carried out in the past is the whole subject of consumer education, as well as physician education. I think there is much more we can do in the future in terms of educating consumers about good drug usage than we have in the past. There are things that we are doing, but obviously we have not done enough at this point in time.

At this point in time you are right, the doctor has that right under the law to utilize drugs as he sees fit, and other than for the legal route, such as malpractices and suits, et cetera, there is not a great deal that can be done in this point of time.

Senator KENNEDY. I'd like to emphasize this point. The doctor has a legal right actually to prescribe a drug for a use for which it has not been approved by the Food and Drug Administration, does he not?

Dr. EDWARDS. That is correct.

Mr. HUTT. That is under Federal law. There may be applicable State laws.

Senator KENNEDY. State laws are another matter. People treated in Massachusetts may be handled differently than those in Wisconsin. That is not good. Now as I understand the situation, you approve a drug for a certain use. But if a doctor wants to prescribe that drug for a use that has not been approved by the Food and Drug Administration, he has the legal authority to do so, and the patient himself is really dependent upon the intelligence and good will of the doctor, and not upon the kind of research done by the Food and Drug Administration.

Dr. EDWARDS. I think that basically is correct, yes.

Congress recognized a patient's right to seek civil damages in the courts if there should be evidence of malpractice, and declined to provide any legislative restrictions upon the medical profession in this regard. Nor do I believe that the Food and Drug Administration should control the practice of medicine. This would unquestionably hinder, rather than promote, good medical care for the country. We cannot, in good conscience, require that a physician watch a patient's condition worsen because the package insert provides for only a low dose of the drug or contains an applicable warning or contraindication. What is needed is the promotion of better prescribing of drugs by such measures as continuing education of physicians, peer review mechanisms, and the use of effective communications between FDA and the medical profession. In short, we must increase the physician's sense of professional responsibility and judgment, not place him in a rigid mold.

Senator KENNEDY. What about a situation in which the doctor is just practicing poor quality medicine? Who is going to protect the patient or the consumer in that case?

Dr. EDWARDS. I think, Mr. Chairman, there are probably two things that have to be considered in a case like that. I think, No. 1 licensure, I mean State licensure laws should be looked at.

Second, peer review. I think there should be a peer review system in this country that eliminates this kind of medical practice.

Your staff have expressed particular interest in DepoProvera. I believe it will be helpful to review FDA's actions with respect to this drug.

DepoProvera is a derivative of progesterone that is administered intramuscularly in the treatment of endometriosis and as adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial carcinoma. It was approved for marketing for endometriosis in 1960, and for metastatic endometrial carcinoma in 1972.

DepoProvera is used for contraception in a number of countries and has been investigated for this indication in this country under a Notice of Claimed Investigational Exemption for a New Drug since 1963.

In 1970, studies in dogs revealed that DepoProvera produced mammary tumors. Similar studies in monkeys have been negative. At that time, contraceptive studies with DepoProvera under the IND were severely limited and the patients under study were required to sign an expanded written informed consent form, which among other things, included a statement pertaining to mammary tumors.

In addition, the FDA and its Obstetrics and Gynecology Advisory Committee felt that further long-term human metabolic studies were necessary on this agent. Accordingly, the committee recommended that the ongoing human studies continue in appropriate patients and agreed with the continued use of the drug under the conditions spelled out in the patient consent form.

The reason that investigational drug studies for contraception were permitted to continue was that DepoProvera represents a unique form of systemically-administered contraception which needs to be administered only once every 3 months. As can be seen by review of the patient consent form, its use is intended for a very restricted patient population; i. e., those who have tried all other birth control methods without success. In this group, it is felt that its known benefit outweighs its theoretical risk since no other alternative therapy is available.

In 1972, some of the mammary nodules in dogs were found to be malignant. The investigators were so informed and the patient informed consent form revised to include this new information. The significance of these dog findings to humans is not known. At this time, the problem was again discussed with our Advisory Committee. The committee made certain recommendations with respect to the labeling and consent forms and stated that although approval of DepoProvera for unrestricted contraceptive use should not be given, the IND should remain active because no other injectable contraceptive is available or forthcoming.

Since DepoProvera is currently available on the market for other approved indications, it is possible that patients are receiving the drug for contraception outside the IND despite the current labeling which discusses the tumorigenicity and indicates that its contraceptive use is still investigational. Accordingly, we continue to confer with our Advisory Committee on this matter and the next meeting is scheduled for later this month.

Senator Kennedy. You were good to come up and testify this morning. I understand you have some time problems and you will not be able to stay for the entire course of the hearings. During the course of this morning's we are going to hear testimony about the widespread use of DepoProvera in the State of Tennessee, as a contraceptive. There are indications that it is also being used for this unapproved purpose in other parts of the country.

Does this concern you?

Dr. Edwards. It certainly does concern us. This is obviously not the first drug which we have run into which was being utilized outside the FDA approval. It does concern us in a very real sense, and of course we are trying the best we can to communicate this to the medical profession.

Senator KENNEDY. What can you do about it?

Dr. EDWARDS. We can investigate individual cases of this happening, but in terms of dealing with the overall big problem, I think it is a matter of better communications with the medical profession trying to stimulate local or State interests in trying to have more peer review and control over this kind of prescribing.

Mr. Hutt brought out, as I mentioned earlier in my testimony, that an initial step was taken in this regard, on August 15 of this past year when we again issued our interpretation of the IND regulations again for the practicing profession.

Senator KENNEDY. As you point out, you are really dependent upon the local groups. There is very little you can do statutorily.

We invited the Tennessee Medical Societies to come up here, and they chose not to appear. We have a real problem here. You are obviously very limited in what you can do. You have to leave regulation up to the various societies, and it is a very mixed bag as to what any of them are really doing.

Yet we are finding, and I think we will see during the course of these hearings, that this is a widespread problem.

Would you continue?

Dr. EDWARDS. Mr. Chairman, just for the benefit of the record, may I ask Mr. Hutt to enumerate the specific things that we can do.

Mr. HUTT. In the August 15 proposal we listed eight specific steps that we could take in order to curb the unapproved use of approved new drugs. I will simply summarize them.

One is to require revision of the package insert to add a specific contraindication or warning against that unapproved use. This of course we have already done.

Senator KENNEDY. That is on the bottle, or package, is it?

Mr. HUTT. That is in the package insert. It is not on the bottle. The package insert is part of the labeling and accompanies each bottle that goes to physicians and pharmacists. It is a form of our communication with the medical profession.

Second, we can require the manufacturer to obtain and submit the data available to either approve or disapprove that particular use of the drug. Of course we are doing that under the IND here.

Third, if there is sufficient evidence available we can then require the package insert be changed to approve that particular use of the drug.

Fourth, we can require that the package insert be changed to state that the drug should not be refilled, if refilling of the drug creates a problem of abuse, for example, with certain types of drugs. That is not applicable here.

Fifth, we can change the package insert and change the method of approval of the drug to restrict the channels of distribution.

It might be possible, for example, to require that it be distributed only through hospitals, rather than to be available to every pharmacy. We have recently taken this approach with respect to methadone in order to restrict its channels of distribution.

I do not know if it is necessary to go into all of these, but the final and the most drastic step that we can take, Senator, would be to disapprove the entire new drug application and remove the drug from the market. This is obviously a very drastic step, and I do not think would be justified in this instance in light of the very essential uses that exist.

Senator KENNEDY. I think it would be useful if you met with some of the staff people of the committee and go over at least some of the kinds of information that have been developed to see what can be done.

Dr. EDWARDS. Mr. Chairman, your committee also indicated interest in the post-coital use of Diethylstilbestrol. This agent is a synthetic estrogen which has been available for over 30 years for various gynecologic indications. We have previously testified before this committee concerning the association of this drug with adenocarcinoma of the vagina and cervix. As you know, warnings were issued in the form of a drug bulletin and the labeling and contraindications for DES now reflect this association.

Use of DES as a post-coital contraceptive is fairly recent and has been proceeding without the submission of Investigational New Drug Applications because of the ready availability of the drug on the market.

On December 10, 1971, information available at that time regarding the use of DES as a "morning after" contraceptive was presented to the OB-Gyn Advisory Committee of the FDA and they were specifically asked if, in their opinion, they felt there was sufficient evidence of safety and efficacy for the use of DES post-coitally in the prevention of pregnancy. The concensus of opinion was that while the available information on the post-coital use of estrogens provides "some" evidence for their efficacy as well as for the relative safety of this regimen, these data would not qualify to fulfill the requirements of a New Drug Application.

At the next meeting of the OB–Gyn Advisory Committee on March 17, 1972, a member of the committee reported the results of the workshop. He pointed out that more experience was available for DES than for other estrogens and that perhaps sufficient experience was available for DES to support the indication in the package insert of its use in a post-coital regimen.

The topic of the post-coital use of DES came up again at the October 20, 1972, meeting of the OB–Gyn Advisory Committee at which time a recommendation was made that the Committee advise the Commissioner that it feels he should communicate to the medical profession the Committee's concern over the widening, but not indicated, usage of DES as a post-coital contraceptive.

At the January 26, 1973, meeting of the OB–Gyn Advisory Committee the use of DES and other estrogens for post-coital contraception was again brought up and the committee was again asked whether the post-coital use of DES could be approved on the basis of available information for its safety and efficacy. A panel of experts had been invited to present their experience to the Committee and representatives of consumers groups were also given the opportunity to present their views.

It was the unanimous conclusion of the Committee members that there exists now substantial evidence for the effectivity of DES in preventing conception by the post-coital administration of 50 mg.—(2×25 mg.) daily for five consecutive days initiated within 72 hours after exposure. It was also the unanimous opinion of the Committee that for this regimen and dosage there is no evidence for a significant risk to the patient, except for some immediate minor side reactions, and that a carcinogenic potential from this dosage has not been proven. However, because the possibility of a harmful effect on the fetus either from a pregnancy existing at the time of treatment from a previous exposure or resulting from a patient failure during treatment, an early abortion induced by conventional means should be seriously considered even though an action of this kind on the fetus is not known to exist.

Let me say that this was a recommendation of this particular Advisory Committee.

On the strength of these conclusions the motion was made and passed, to recommend to the Commissioner approval for the use of DES postcoitally as a contraceptive under the outlined conditions and circumstances, with the provision that this usage is to be considered as an emergency treatment only and that it should not be considered as a method for birth control with continuous and frequent repeated therapy.

Senator KENNEDY. What is an emergency situation?

Dr. EDWARDS. Usually after rape.

Senator KENNEDY. Restricted to that?

Dr. EDWARDS. Again I think it has to be emphasized that there are very few emergency situations of this kind.

Senator KENNEDY. Would you be concerned about the extensive use of this drug in university health departments, if you knew that were to be the case?

Dr. EDWARDS. We are concerned about that. We certainly had reports that it is being widely used. We are trying to investigate the extent of this abuse.

Dr. Simmons might be able to speak more specifically to that. I think the point is that we are well aware of it, we are trying to investigate it, to see just what degree it really exists. But we are certain it has been abused.

I think at some point in time a very real question will have to be asked, if this is being abused, will we have to eliminate the drug entirely?

Senator KENNEDY. What would be your only potential remedy?

Dr. EDWARDS. Mr. Hutt referred to the six or eight alternatives we have; but obviously, if we cannot control it, the most drastic action we can take is to eliminate the drug entirely from the marketplace.

Senator KENNEDY. You would be prepared to recommend that if these other steps were not successful?

Dr. EDWARDS. I think at that particular point in time, Mr. Chairman, we have to sit down again with the experts on this particular committee and weigh the benefits and risks and make a decision in this regard.

Senator NELSON. I understood you to say that there was no evidence of carcinogenic risks in this drug.

Dr. EDWARDS. I said that we were at this point in time, Senator, unable to evaluate that risk. We have evidence that certain mammary tumors have been produced in dogs. The relationship, as you know, between the occurrence of mammary tumors in dogs, and how you extrapolate that to man is a difficult subject.

Senator NELSON. I thought in your prepared text a few moments ago you stated that there is evidence of carcinogenic risk. Did I misunderstand you?

Dr. EDWARDS. No. I beg your pardon. I mentioned at the very beginning of the discussion of this particular drug—it was discussed earlier—that adenocarcinomas have occurred in offsprings of females that received DES at the time they threatened to abort. But I would emphasize we are talking about massive doses over further extended periods of time, in the case of threatened abortions.

Here we are talking about a five day period in which it is given

Senator NELSON. DES is available by prescription in the marketplace generally now, is that right?

Dr. EDWARDS. That is correct.

Senator NELSON. I do not want to repeat anything, but did you discuss the package labeling indications for its use before I arrived this morning?

Dr. SIMMONS. We did not, Senator, but we have a package insert here. It is for general use as an estrogen for wide variety of indications, and it is not approved at this time for post-coital use. This has been recommended to us. What the Committee concluded was that for this particular use, which they are recommending, they see no hazard to the mother. They state there is a potential risk to the child, and therefore the mother should consider the possibility of abortion should the drug fail.

Senator NELSON. You say you have not covered its indicated uses this morning?

Dr. SIMMONS. We have not gone into that.

Senator NELSON. Do you mind if I ask about that?

Senator KENNEDY. Do you want to let Dr. Edwards finish his statement first?

Senator NELSON. Sure.

Dr. EDWARDS. I will finish right away, Mr. Chairman.

This drug is just one example of a number of complex questions which faces the agency and its advisors in the course of drug research and development. The difficult benefit-risk judgments are well illustrated by this drug.

With that, Mr. Chairman, I will conclude, and we will answer any questions that you wish to pose.

Senator KENNEDY. Do you want to finish your questions, Senator Nelson?

Senator NELSON. What are the package label indications for its use?

Dr. SIMMONS. I will read them to you. It is indicated as therapy in states of estrogen deficiency, associated with menopausal syndrome and female castration, and for the prevention of post partum breast engorgement.

Senator NELSON. For what?

Dr. SIMMONS. Post partum breast engorgement. There are about 10 other indications here of estrogen deficiency where it might be used, such as vaginal problems and things such as that.

Senator NELSON. Is that the only drug available for those indicated purposes?

Dr. SIMMONS. No. There are a number of estrogens. This is one of the class of drugs, all of which are available for those indications.

Senator Nelson. When used for the indicated purposes, does the therapy indicate an extended use repeatedly over a long period of time?

Dr. Simmons. That is an allowable use, and there is a precaution which indicates patients receiving the drug should be under continuous medical supervision. Women's breasts and pelvic organs should be examined before treatment is begun and at intervals during therapy. It gives a number of adequate precautions for safe use of the drug for the approved indications.

Senator Nelson. Do the other available drugs in that therapeutic category have a history of any carcinogenic indications at all?

Dr. Simmons. They all do, Senator. This is the only one that has shown the particular offspring adenocarcinoma problem in female offspring of mothers treated with diethylstillbestrol (DES) during pregnancy. All estrogens are known to be tumorogenic in three or four species of animals, as is DES.

Senator Nelson. Have any studies been done at all of the nature and character of its use, as has been done with a number of other drugs such as anti-infective. That is, studies of their misuse and overuse?

Dr. Simmons. Yes, we have looked into that in a number of college campuses. We have visited the University of Michigan and conducted a study there on its use.

We are also looking into the extent of its use as a postcoital contraceptive elsewhere with the help of our committee.

Senator Nelson. What was the use on the university campus?

Dr. Simmons. That was for postcoital use to prevent conception. It was contraceptive use.

Senator Nelson. That was the general practice on the campus?

Dr. Simmons. I would not term it that, Senator.

Senator Nelson. Was it dispensed by the infirmary, that is, by the institution itself?

Dr. Simmons. That is right.

Senator Nelson. How would you describe its use?

Dr. Simmons. I do not know enough about its general use on that campus. It was used in some women who would come in and give a history of having a sexual exposure and did not want a chance of conception. It was prescribed for those. I imagine it was prescribed for cases of rape. I do not know the extent of that.

Senator Kennedy. We are going to document that DES is used extensively in this country at tomorrow's hearing.

Dr. Simmons. The main thing to keep in mind is that our Advisory Committee, in recommending its approval for emergency use very carefully points out that it should not be used as a contraceptive use for other than emergencies. It is not a contraceptive for somebody who is trying to prevent a pregnancy over a long period of time. In that case its hazard outweighs its benefit.

In the other instance it is felt that it is safe.

Senator Nelson. You are aware of the studies showing the widespread overuse and misuse of anti-infectives for nonindicated situations. It was found in one study that in only 12.9 of the cases were this category of drugs used rationally. In one hospital anti-infectives were administered prophylactically in 80 percent of the uncomplicated hernia operations. When you get to a drug of this kind that has a proven history of carcinogicity, why should you not at least require the reporting on it as you do with a narcotic, for example?

Dr. Simmons. It would probably be almost as much a legal question as a medical question, Senator. We know the problems with this drug. They are increasingly well documented.

We have passed that information on to physicians, both through a drug bulletin—600,000 of them went out as soon as we know of this problem—and through labeling which has been corrected to indicate its potential problems.

I am not sure what else we would gain by further reporting.

As I said, we do know the problems associated with this drug now.

Senator Nelson. You had to cut down the use of amphetamines, did you not?

Dr. Simmons. Yes; but that is under the drug abuse amendment, and this kind of drug is not covered by that. That is a legal question, I suspect, more than medical.

Those are drugs abused in another way.

Senator Nelson. Well, they are used for nonindicated cases, right?

Dr. Simmons. Right.

Senator Nelson. Well, that is what this drug is being used for——

Dr. Simmons. Yes. The drug abuse provisions are more addressed to narcotic and mind altering drugs, and I do not believe address this particular kind of compound.

Dr. Edwards. I agree with you. I think drug abuse is drug abuse, by whatever name you want to call it. Although we have not thought about it along the lines you have just suggested, let me just say that we are certainly open to any suggestions that might help us better control these drugs and be assured, as I said at the beginning, at this particular point in time our major responsibility is to be sure that the package insert, the labeling on these drugs, is accurate and up to date and provides the doctor, the physician, with the best information that is currently available.

Senator Nelson. As we know, the doctor does not get the package inserts. That goes to the druggist, and he may never see it. As a matter of fact, if the physician had a reliable source of information you would be willing to get rid of the package insert, would you not?

Dr. Edwards. All the advertising, as you know, has to agree with the labeling, so it does get to the physician one way or another, not perhaps to the degree that you and I would like to see it happen, but nevertheless I think this is improving. But again it is a tough issue to face, and we are trying to develop our communications with the profession as best we can.

Senator Nelson. What troubles me is that this drug is carcinogenic to the fetus. It is apparently being used prophylactically. Do you not have enough experience with the history of warning the medical profession about the misuse, overuse, or the use of drugs for nonindicated cases to realize that the responses are not very good.

One of the classic cases that you have testified on is chloramphenicol, which is being administered to about 4 million people a year in this country, although there might have been 5,000 or 10,000 indicated cases at best. In other words, 90 to 95 percent of the people receiving the drug were receiving it for nonindicated cases.

How do you expect to get this warning to the medical profession that they should use it only under certain circumstances or not at all? That is what puzzles me.

Dr. Edwards. I would not attempt to sit here and tell you that I think we can get to all of the medical profession. I think we can thank the dear Lord that the bulk of the medical profession are conscientious and try to practice good medicine. Nevertheless, there are some that do not, and we have got to come up with ways in which the chairman and I discussed a little earlier that will be adequate to upgrade the quality of the health care in this country, particularly among those who are not observing the rules and regulations.

Senator Nelson. Nobody is worried about the doctor who relies upon scientific literature to prescribe. What we are worried about is the doctor who relies upon, as many do, the detail man and the promotional advertising in the medical journals and magazines. That is the one we have to worry about, not the one who relies upon the scientific literature.

So if they are not relying upon scientific literature, how do you communicate with them? You have not been very effective in the past, as you know, even though you genuinely try to convince them on chloramphenicol. I think your statistics show that it is still widely overprescribed.

Dr. Edwards. Even in the case you brought up and the case of amphetamines, I think more and more we are getting to the medical profession. I am not, by any stretch of the imagination, suggesting we have solved the problem. We are improving.

I think amphetamines are a good case in point. Once we went to the doctor with the information and pointed out the hazards and problems associated with their use, there was a tremendous decrease in the use of this particular class of drugs.

There are other drugs in which the same thing, I think, can be adequately shown. Nevertheless, there is still a big job to do, and I think our drug bulletin is a major step forward, the fact that we are cracking down on the advertising, and the fact that promotional literature has to conform to the labeling, are slowly getting the right kind of information into the hands of the doctor.

Unfortunately there are those who want to ignore it, that is a problem.

Senator Nelson. Thank you.

Senator Kennedy. Senator Schweiker.

Senator Schweiker. Thank you, Mr. Chairman.

Dr. Edwards, I would like to just go back to the part of your testimony relating to drugs for children. You point out that the metabolic effect on children is sometimes quite different from adults, and thus you either are working on or already have some recommendations about how to deal with drug testing on children.

Again, what is your position?

Dr. Edwards. Over the years the drugs have not been tested particularly on children. We have been working very closely with the American Academy of Pediatrics, which is certainly one of the more responsible organizations, in trying to develop specific guidelines as they relate to the use of investigational drugs in children. If you want to get into the specifics of that, maybe Dr. Simmons could give you more information.

Senator SCHWEIKER. What I had in mind is, when you approve a drug for general usage, do you now test for children or is that something that you are planning?

Dr. SIMMONS. This is evolving, Senator. In the past that testing was not required. There was a classical line used in the labeling, "this drug has not been tested in children and its safety is unknown."

That same line is in for pregnant women, "The safety of this drug for pregnant women is unknown."

The major change that has come about since Commissioner Edwards has instituted this change is to require a drug that is likely to be used in a child to be tested in a child. Thus, the "miniature adult" concept, which so long prevailed, has been broken down now, as the insistence of the pediatric profession and the Food and Drug Administration. Now drugs in testing are required to develop appropriate studies in children in whom they are likely to be used.

There are still many drugs that were approved prior to this policy that have not been adequately tested.

Senator SCHWEIKER. Under your new policy when you approve a new drug which has not been tested on children because you do not expect it to be used for children, is that information available? Would a doctor know that while it may be intended for adults, he should not use it on children?

Dr. SIMMONS. It is usually spelled out in the labeling that the drug is contraindicated in certain age groups or has to have a certain dosage or precautions in a certain age group or has not been tested adequately in a certain age group.

There are a variety of ways that we point that out.

Senator SCHWEIKER. He could still, notwithstanding the label, could go ahead and use it on children if he wanted to.

Dr. SIMMONS. That is correct.

Senator SCHWEIKER. On page 10, Commissioner, I would just like to understand the mechanics of the approved and nonapproved use of drugs.

A marketed drug that has been approved by your agency, and you in that situation describe certain approved uses, could be utilized for a non-approved purpose by a physician with no oversight or responsibility on your part, because, as I understand it, that is outside your jurisdiction.

Dr. EDWARDS. That is correct.

Senator SCHWEIKER. What recourse does society have or what recourses exist to cover those deficiencies——

Dr. EDWARDS. I think unfortunately the only recourse today is malpractice.

Senator SCHWEIKER. There is no other trade or association approach to this?

Dr. EDWARDS. I must say that many institutions have established peer review operations. Some of the groups like the Kaiser plant out on the West Coast, they have peer review kinds of organizations—the San Joaquin Foundation out in California. There are a number of group practices that have their own peer review type of monitoring.

As a general rule, it is not applicable. In a number of hospitals of course, you have some kind——

Senator SCHWEIKER. When a doctor uses a drug for an unapproved use, is he in a technical violation of any Federal regulation?

Dr. EDWARDS. No.

Senator SCHWEIKER. So there is no present law covering that?

Dr. EDWARDS. No.

Senator SCHWEIKER. On page 15 of your testimony referring to DES, do I understand when you refer to the researcher article appearing in the journal of AMA, that this was a case in which a researcher on her own, without your procedure for an investigative drug, was utilizing this drug for a nonapproved purpose and researching it?

Dr. EDWARDS. That is correct.

Senator SCHWEIKER. Again, was that not a technical violation?

Dr. EDWARDS. No. She has that right under the present law.

Senator SCHWEIKER. Because it was approved for other purposes, is that the difference?

Dr. EDWARDS. Mr. Hutt, our general counsel might want to speak to that issue.

Mr. HUTT. The way the law reads, if she prescribes it from the local pharmacy, it would not require an IND plan. If she wrote the company and asked the company to ship the drug to her for purposes of an investigation, then an IND plan would be required. The way the statute reads it is on shipment in interstate commerce for the particular use.

Senator SCHWEIKER. So she could get it from her local pharmacy, but could not go to the drug house to get it?

Mr. HUTT. That is correct.

Senator SCHWEIKER. Pretty big loophole?

Mr. HUTT. Yes, sir; it is.

Senator SCHWEIKER. You refer on the next page to the use of a package insert for DES. I would like to understand where that insert goes and who sees it. I know Senator Nelson was questioning on this point.

Dr. EDWARDS. It goes several places. Number one, it goes literally in the package, which the pharmacy has.

Senator SCHWEIKER. Does it get beyond the pharmacist?

Dr. EDWARDS. In some instances the doctor gets the package insert and in some instances he does not.

When he does not, there are other places where the doctor can pick up this information, for instance in the PDR, which is a reference book that most physicians have on their desk, the labeling is indicated in the PDR's, when he looks at the drug, it is there in full.

All of the advertising on prescription drugs has to conform to the labeling, has to have all of the contra-indications, dosages, and so forth. There are other exposures to the labeling other than just the package insert per se. If he does not get the package insert, he can still find out this information.

Senator SCHWEIKER. I would guess that in the overwheming majority of your drug prescriptions today the doctor has not seen the package. He has not been the middleman in this situation, only the druggist has. And, the druggist customarily does not provide the package insert, is that not correct?

Dr. EDWARDS. That is correct. I think we have to say that most prescriptions prescribed by physicians are routine. I mean they prescribe them over and over and over again. So it would be to no particular advantage to have the physician read it everytime he prescribed the drug. He should be very familiar with the indications, the counter-indications, and the problems that that particular drug might present.

So there are some extenuating circumstances is all I am saying. Each time you do not have to take a look at the package insert.

Senator SCHWEIKER. Would it not make some sense perhaps to put on the bottle itself some of these facts so that the average person would know a little bit about what it cannot be used for?

Dr. EDWARDS. I think we are moving more and more in this direction, to varying degrees. Several years ago, as you know, we did come forth with the first package insert for the patient, that was with the oral contraceptive drugs. I think there are a number of groups that are looking into the possibility or the feasibility of putting on the bottle itself some of the indications, contra-indications, and things that ought to be looked for on the label.

These are things that certainly warrant exploration.

I might add that we are considering a patient package insert for several other drugs right now.

Senator SCHWEIKER. In the unapproved use of drugs for children, what is the informed consent procedure?

Dr. SIMMONS. The procedure now is that the legal guardian would give informed consent for a child not of age. The procedure for non-approved use, when during the practice of medicine a physician chooses to give a drug to a child in which the package insert states, under use in children, "this agent should not be used in children since adequate data to establish safe conditions of use are lacking." That is a standard line. Then the physician must make the choice of whether he would or would not observe the statement.

Senator SCHWEIKER. The parent of the child would not have anyway of knowing that?

Dr. SIMMONS. That is right.

Senator SCHWEIKER. Unless the doctor conscientiously provides that information.

That is all I have, Mr. Chairman.

Senator KENNEDY. Thank you very much, Mr. Simmons.

Senator NELSON. I have another question. Senator Schweiker was pursuing the question of using drugs for nonindicated purposes, and you responded that the package insert is available. The doctors do not have to see it every time because they prescribe over and over again.

You are well aware of the study done by Dr. Lasagna and Dr. Stolley on medical practice respecting the common cold in which 95 percent of the physicians prescribed a drug for the common cold, and 60 percent of them prescribed an anti-infective. The anti-infective is not indicated for any of the viruses that cause the common cold.

So what this study shows is that about half of the medical profession prescribe anti-infective drugs for non-indicated cases. That is a serious situation certainly. A person perfectly healthy going to a doctor and receiving an anti-infective for a nonindicated case exposes himself to the possible side effects. It is this kind of dramatic statistics that ought to alarm the FDA and the AMA. If there is any way in the world to alarm the AMA about medical practice, that ought to do it.

We keep talking about this subject. We were raising the same questions 6 years ago, and each successive study seems to indicate the same kind of misuse of drugs.

Do you really believe that we are tackling this in an effective way?

Dr. Edwards. I certainly do not feel that we have attacked it adequately. I think that we are improving. I think that the misuse of the antibiotics, in spite of what anybody says, is less today than it was 3 or 4 years ago. The American Medical Association has just recently, I think at the suggestion of the Food and Drug Administration, indicated they are having a major conference in March with all the major specialty organizations and other outside organizations to really look into this overuse and misuse and abuse, of the antibiotics.

Again, it is a problem. I am not for a moment condoning the practice of treating patients with a common cold with antibiotics. The situation is improving, but not fast enough.

Senator Nelson. You are aware that the medical society just met and abolished their conscience by disposing of their Council on Drugs, which was the one scientific body that the AMA had to provide some guidance and education for the profession in the use of drugs. They abolished it after Council on Drugs created the prescribing manual, which is exactly what was needed by the profession. However, once they put out the prescribing manual, it caused lots of friction between the manufacturers and the doctors who wanted to be sure the drugs were properly prescribed. The AMA, then, abolished the Council on Drugs and turned over to the AMA staff the responsibility for revising the manual.

That is going backward, not forward. I think you will agree that that is not progress. But that is not your fault. I just say I doubt very much whether we are going forward very rapidly.

Would you agree that the Government ought at the very least to publish a compendium? The HEW's task force of prescription drugs recommended that a compendium be published. Do you think it would serve a useful purpose?

Dr. Edwards. I think there should be a compendium, Senator. I think the Federal Government should see to it that there is a compendium available to physicians. There are others, other than Government, that could conceivably publish it.

Senator Nelson. Let me rephrase the question. Do you agree that a compendium is a necessity for the medical profession?

Dr. Edwards. Yes. Again I think I have qualified only to the extent that different people have different ideas of what really a compendium really is. I think there should be a major drug reference like this for every physician. I do not think there is any question about that.

I think we have to be sure that it does not become such a compendium that it is so big and so voluminous that nobody ever uses it. That is why I think, for instance, the AMA's drug—what do they call the book—drug evaluation studies—is probably a pretty good book.

Senator Nelson. Well, we are talking about two different things now. We probably need a prescribing manual, a handy prescribing manual authoritatively prepared, and a compendium.

Dr. Edwards. I think they fit sort of hand in hand.

Senator Nelson. So we did have the manual, and then the Council on Drugs that prepared it has been abolished.

I will be interested to see what the American Medical Association puts out next time and whether they use the words "rational" or "irrational" or "not recommended," over the objections of the PMA.

[The prepared statement of Dr. Edwards follows:]

STATEMENT BY CHARLES C. EDWARDS, M.D., COMMISSIONER OF FOOD AND DRUGS, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman:

We are pleased to appear before you today to discuss the policies and programs of the Food and Drug Administration with regard to the safeguards provided for humans participating in clinical drug trials leading to the development of new drugs.

It should be understood at the outset that this is a difficult and complex subject with serious scientific, moral and ethical considerations. We therefore sought guidance in this area from an Ad Hoc Committee on Ethical Criteria in Drug Evaluation of the National Academy of Sciences. This Committee itself had difficulty in providing definitive answers to questions in this area and recommended a:

> "conference in which these legal, ethical and humanitarian matters might be considered further either by the National Academy of Sciences, through its Drug Research Board, or by the Institute of Medicine, or both."

We understand you are particularly interested in the procedures associated with the approval of new indications for a drug already approved for other indications. We will address this question as well as your interest in the monitoring of the uses of approved drugs for unapproved uses, and provide information on two specific drugs in which committee staff have expressed interest.

Under the Federal Food, Drug, and Cosmetic Act a new drug may not be shipped in interstate commerce without an approved new drug application (NDA). Basically, FDA approves an NDA if adequate and well-controlled data extablish that the drug is safe and effective for the conditions prescribed, recommended or suggested in its labeling. As part of the approval, FDA approves the labeling of the drug which must accompany the drug and fully disclose the intended uses, dosage levels, warnings, side effects, and contraindications for the drug. The advertising and promotion of the drug must be limited to the indications approved in this official labeling.

There is an exemption, of course, for the investigational use of drugs to permit sponsors to develop the needed data to support marketing and determine dosage levels, routes of administration, warnings, adverse reactions, contraindications, and other relevant prescribing information. The investigations must be sound and well controlled and instituted only pursuant to a protocol design submitted to FDA for review. This protocol is officially a "Notice of Claimed Investigational Exemption for a New Drug," more commonly referred to as an "IND."

Need for Clinical Study

Perhaps the most critical point that can be emphasized this morning is the real dilemma that exists with regard to any research or investigational study. At the present time, there is no species of animal or "in vitro" laboratory test system that can be relied on alone to be completely predictive of what to expect in man. In other words, no matter how much animal or laboratory data we can collect, at some point we must address ourselves to the question "What does this data mean for man and how will a human be affected by this drug?" This is why clinical studies are necessary. If we should ever decide that clinical studies cannot be undertaken, then we effectively terminate further drug development and progress in medicine. The surgeon will no longer be able to develop new techniques, the internist will no longer be able to achieve progress in improved approaches to diagnosis and treatment of illness and disease, and FDA will no longer be able to determine the safety and effectiveness of new therapeutic agents. Until we have an animal or laboratory system that is perfectly predictive for man, we are and will be dependent on adequate and well-controlled clinical research.

Studies in Children

In this same general context one should discuss the use of investigational drugs or other new therapeutic approaches in children. There is, understandably, a natural reluctance on the part of some scientists to conduct studies in children. But the fact is that when children are sick, they too may need drugs and it would surely be unethical to administer to children drugs which have not been studied in children. Infants and children often do not metabolize drugs as adults do. Moreover, it is usually not possible to predict the correct dose of a drug for a child merely by regarding him as a miniature adult and lowering the dose proportionately.

Experts in pediatrics and in pharmacology have concluded that drugs must be studied in children before they are used in children; in fact, FDA requires that drugs be studied in all age groups for which a drug is intended.

Dr. Shirkey, Professor and Chairman of Pediatrics, School of Medicine. Tulane University, and chairman of the former American Medical Association Council on Drugs, has also expressed his concern in this area:

> "Today over half of the new drugs have not had adequate studies in children yet the drugs are released and available for physicians. These drugs are prescribed for children.
> The plea today is to study the drugs which are already available and are widely used with the refined methods which could give tremendous information if this were supported and to study new drugs as Congress intended."

Clearly when a drug or other therapeutic approach is studied in children, the children should be expected to benefit from the course of treatment being studied. Other studies on the effects of the drug may also be done simultaneously and recorded, but a benefit to the patient should exist to justify the study. The FDA has such a working policy on the use of investigational drugs in children and is working with experts of the American Academy of Pediatrics to develop guidelines for drug testing in children.

The Federal Food, Drug, and Cosmetic Act

Congress has many times acknowledged both the need for continued clinical study as well as the necessary safeguards that should be associated with it. The Federal Food, Drug, and Cosmetic Act provides for clinical study with appropriate provisions for informed and safe participation.

The 1962 Drug Amendments to the Federal Food, Drug, and Cosmetic Act required FDA to exercise strict control over the use of investigational drugs undergoing clinical trials. The IND procedure offers comprehensive control of the developmental testing of drugs in this country and insures that the proposed studies are justifiable and do not expose human beings to undue risks. Our regulatory process also requires that the studies be well controlled and therefore meaningful.

Patient Consent Regulations

A number of regulations have been promulgated by FDA pursuant to its legal authority to protect the human research subject participating in drug studies. Among other things, the 1962 Drug Amendments specifically required that consent be obtained except when not feasible or when, in the judgment of the investigator, it is contrary to the best interests of the patient. In 1967, FDA clarified and strengthened this statutory provision by regulations requiring written consent in the first two phases of human clinical trials and a documentation if oral consent is obtained in place of written consent in Phase III.

Initial Screening of Studies

Of signal importance is FDA's action in 1970 to further reduce the possibility of patients being exposed to unwarranted risk. Prior to 1970 investigational use of a new drug, with some exceptions, could begin immediately upon the filing of an application for an exemption to the New Drug provisions of the Federal Food, Drug, and Cosmetic Act. The new regulation provided for a 30-day delay before clinical studies could be initiated in order to allow for a preliminary screen of the proposed study to assure that the drug has been adequately studied in laboratory animals and would be studied under a scientifically sound protocol that would not expose human subjects to an unwarranted risk.

Disqualification of Investigators

Also pursuant to the 1962 Drug Amendments, the FDA has acted to "disqualify" clinicians because of improper and unethical practices. A program of surveillance of clinical investigators began in 1967, and specific formal procedures for such "disqualification" of clinical investigators were established in 1968. Since then, sixteen investigators have been disqualified and twenty have been reprimanded.

When an investigator is disqualified, he is ineligible to receive investigational drugs and all the sponsors employing the individual as an investigator and appropriate Government agencies are notified of this disqualification. The data generated by a disqualified investigator cannot, of course, be utilized by the manufacturer in support of his application for marketing approval. In the case of reprimands, sponsors are routinely notified of the investigators' shortcomings since these are usually indicative of poor monitoring by the sponsor. It should be noted that criminal cases have been filed for fraudulent data submitted and one such case has recently been referred to the Department of Justice and is now under their review.

Increased Surveillance of Investigators

Good investigational practices are, of course, intimately related to good monitoring by the sponsors of the study. For the coming year, FDA has designed a program to permit a more precise determination of the quality of such monitoring in this country. Some 8-12 studies on new significant compounds have been selected for intensive surveillance. This is an initial step to improve the existing approach of primarily investigating researchers under suspicion of violation. The increased coverage provided by this program should give a truer picture of the state of affairs of clinical investigations carried out under investigational new drug (IND) regulations in this country. If serious shortcomings are found, the inspections can provide a basis for developing appropriate means to address this problem. This should result not only in protection of the public directly exposed to the drugs but also to improvements in clinical testing. Together we believe this will encourage approval of New Drug Applications with fewer but better clinical studies, and thus benefit the consumer by insuring more prompt entry of good drugs into the marketplace.

Institutional Review Committee Under FDA Regulations

FDA's regulatory procedures have also been strengthened by providing for local review of studies to determine whether proposed studies are justified in a particular area and to provide a local system of assurance that the study is conducted ethically and in compliance with the law. In 1971, FDA promulgated regulations to require Institutional Committee Review of investigational new drug studies. If such studies are conducted on institutionalized subjects or by an individual affiliated with an institution assuming responsibility, assurance must be provided that an institutional review committee is responsible for initial and continuing review of the study. A review committee must be composed of persons of varying backgrounds (lawyers, clergy, laymen, as well as scientists) and cannot be composed solely of physicians. An intramural FDA committee (the Research Involving Human Subjects Committee) now provides this type of review for all studies involving human subjects which are conducted by FDA.

We believe review by a committee composed of persons with diverse backgrounds offers practical and necessary protection for human subjects. But it must be remembered that such screening of research projects can only be assessed on the basis of currently available information. The appropriateness of a particular study must be judged in the context of the time when it was initiated. Of course all necessary steps must be taken to provide for the reasonable and timely reappraisal of research projects as new scientific information becomes available which might alter the original assessment. These FDA regulations require the Institutional Committee to provide a continuing review of the study at appropriate intervals, but not exceeding one year.

Because of the special problems associated with studies by individual physicians on their non-institutionalized patients, the regulation did not extend this far, but FDA is studying what protection mechanism might be appropriate in these circumstances.

At this time I would like to offer for the record a copy of the FDA regulations I have referred to concerning patient consent, disqualification, institutional review and the 30-day delay interval for IND's.

FDA Contract with Drug Research Board

In other efforts to further examine the many issues raised regarding drug testing on human subjects, a contract was awarded to the Drug Research Board of the NAS-NRC to help define the relative roles of the sponsor and the Food and Drug Administration with regard to clinical investigations. FDA is now in the process of reviewing the report from the NRC Drug Research Board to determine what modifications can be made in the system to improve it further so that investigators are aware of their responsibilities, that research facilities are adequate, that patient followup is appropriate and that consent is informed and voluntary.

Unapproved Uses of Approved Drugs

Your staff have expressed particular interest in regards to procedures for the approval of additional uses or indications for drugs already on the market. Studies of new uses of a drug are also subject to our IND controls. Adequate and well-controlled studies are required to establish the safety and effectiveness of the drug for that particular use. It is illegal to promote and market or ship a drug in interstate commerce for an unapproved use without an IND.

However, the prescribing of an approved drug for an unapproved use by individual physicians in the practice of medicine is beyond the jurisdiction of the FDA.

A proposed regulation issued by FDA August 15, 1972,clearly outlined this issue and I would, at this time, like to offer that regulation for the record. If an approved new drug is shipped in interstate commerce with the approved labeling and neither the manufacturer nor the recipient intends that it be used for an unapproved purpose, the requirements of the Act are satisified. Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the labeling, without informing or obtaining the approval of the FDA.

This interpretation of the Act is required in light of the legislative history of the Act which is replete with statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the law did not purport to regulate the practice of medicine as between the physician and the patient. Congress recognized a patient's right to seek civil damages in the courts if there should be evidence of malpractice, and declined to provide any legislative restrictions upon the medical profession in this regard. Nor do I believe that the Food and Drug Administration should control the practice of medicine. This would unquestionably hinder, rather than promote, good medical care for the country. We cannot, in good conscience, require that a physician watch a patient's condition worsen because the package insert provides for only a low dose of the drug or contains an applicable warning or contraindication. What is needed is the promotion of better prescribing of drugs by such measures as continuing education of physicians, peer review mechanisms, and the use of effective communications between FDA and the medical profession. In short, we must increase the physician's sense of professional responsibility and judgment, not place him in a rigid mold.

Although the Act does not require an individual physician to file an investigational new drug plan before prescribing an approved drug for unapproved uses, or to submit to the Food and Drug Administration data concerning the therapeutic results and the adverse reactions obtained, it is sometimes in the best interests of the physician and the public that this be done. The physician should recognize that when using drugs for investigational purposes, careful account should be taken of the scientific principles, including the moral and ethical considerations, applicable to the safe use of investigational drugs in human patients. When the results of treatment are reported completely and accurately, the data may be helpful to other patients and physicians as well as to the Food and Drug Administration.

If a pattern of unapproved use develops for a particular drug, FDA can take certain actions which are outlined in our August 15th proposal.

Depo-Provera

Your staff have expressed particular interest in Depo-Provera. I believe it will be helpful to review FDA's actions with respect to this drug.

Depo-Provera (medroxyprogesterone acetate) is a derivative of progesterone that is administered intramuscularly in the treatment of endometriosis and as adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial carcinoma. It was approved for marketing for endometriosis in 1960, and for metastatic endometrial carcinoma in 1972.

The drug is marketed in this country and in at least 47 other countries. Most other countries receive the drug from Belgium where it is manufactured.

Depo-Provera is used for contraception in a number of countries and has been investigated for this indication in this country under a Notice of Claimed Investigational Exemption for a New Drug (IND) since 1963.

In 1970, studies in dogs revealed that Depo-Provera produced mammary tumors. Similar studies in monkeys have been negative. However, because of this finding in dogs, Provest, a marketed oral contraceptive containing medroxyprogesterone acetate and ethinyl estradiol was voluntarily removed from the market by the sponsor in 1970, and physicians were notified of the animal findings. At that time, contraceptive studies with Depo-Provera under the IND were severely limited and the patients under study were required to sign an expanded written informed consent form, which among other things, included a statement pertaining to mammary tumors. A copy of this informed consent form is submitted for the record.

In addition, the FDA and its Obstetrics and Gynecology Advisory Committee felt that further long-term human metabolic studies were necessary on this agent. Accordingly, the committee recommended that the ongoing human studies continue in appropriate patients and agreed with the continued use of the drug under the conditions spelled out in the patient consent form.

The reason that investigational drug studies for contraception were permitted to continue was that Depo-Provera represents a unique form of systemically-administered contraception which needs to be administered only once every three months. As can be seen by review of the patient consent form, its use is intended for a very restricted patient population; i.e., those who have tried all other birth control methods without success. In this group, it is felt that its known benefit outweighs its theoretical risk since no other alternative therapy is available.

In 1972, some of the mammary nodules in dogs were found to be malignant. The investigators were so informed and the patient informed consent form revised to include this new information (copy attached). The significance of these dog findings to humans is not known. At this time, the problem was again discussed with our advisory committee. The committee made certain recommendations with respect to the labeling and consent forms and stated that although approval of Depo-Provera for unrestricted contraceptive use should not be given, the IND should remain active because no other injectable contraceptive is available or forthcoming.

In 1970, there were approximately 1,000 patients covered under the IND. This number subsequently dropped to about 600 and following the requirement of the expanded written patient consent form, this number dropped further to a current figure of approximately 140.

Since Depo-Provera is currently available on the market for other approved indications, it is possible that patients are receiving the drug for contraception outside the IND despite the current labeling which discusses the tumorigenicity and indicates that its contraceptive use is still investigational. Accordingly, we continue to confer with our advisory committee on this matter and the next meeting is scheduled for February 22.

Post-Coital Use of Diethylstilbestrol (DES)

Your committee also indicated interest in the post-coital use of Diethylstilbestrol. This agent is a synthetic estrogen which has been available for over 30 years for various gynecologic indications. We have previously testified before this committee concerning the association of this drug with adenocarcinoma of the vagina and cervix. As you know, warnings were issued in the form of a drug bulletin and the labeling and contraindications for DES now reflect this association.

Use of DES as a post-coital contraceptive is fairly recent and has been proceeding without the submission of Investigational New Drug Applications because of the ready availability of the drug on the market.

Following an article by Dr. Lucille Kuchera appearing in the *Journal of the American Medical Association* of October 25, 1971 entitled "Post-Coital Contraception with DES," (attached) FDA decided to pursue the matter of safety and efficacy for this indication. Following publication of this article, a representative from the FDA was sent to visit Dr. Kuchera and discuss with her the results of the study and obtain additional information.

On December 10, 1971, information currently available regarding the use of DES as a "morning after" contraceptive was presented to the OB-Gyn Advisory Committee and they were specifically asked if, in their opinion, they felt there was sufficient evidence of safety and efficacy for the use of DES post-coitally in the prevention of pregnancy. The concensus of opinion was that while the available information on the post-coital use of estrogens provides "some" evidence for their efficacy as well as for the relative safety of this regimen, these data would not qualify to fulfill the requirements for New Drug Application. At that meeting it was proposed that a "working session on the post-coital use of estrogens" be convened between staff members from NIH and the FDA and that the outcome of this conference be presented at the next OB-Gyn Advisory Committee meeting. This proposal was accepted by the Committee and such a workshop was held on February 14, 1972.

At the next meeting of the OB-Gyn Advisory Committee on March 17, 1972 a member of the Committee reported the results of the workshop. He pointed out that more experience was available for DES than for other estrogens and that perhaps sufficient experience was available for DES to support the indication in the package insert of its use in a post-coital regimen. Another Committee member commented that from a scientific point the information (presented at the Workshop) was not substantial, but that the general impression was that this regimen was effective. The OB-Gyn Advisory Committee did not at this meeting make any recommendation one way or another as to the efficacy and safety of DES when used as a post-coital contraceptive.

The topic of the post-coital use of DES came up again at the October 20, 1972 meeting of the OB-Gyn Advisory Committee at which time a recommendation was made that the Committee advise the Commissioner that it feels he should communicate to the medical profession the Committee's concern over the widening, but not indicated, usage of DES as a post-coital contraceptive. This suggestion was implemented by the Committee by outlining the content of the proposed communication:

> "It should state that while there is a wide spread use of DES for this action, this is a nonindicated use, because

> there is insufficient evidence for its efficacy and safety in view of evidence suggesting that it may affect both the user and the offspring surviving ineffective treatment. It should also contain information on what is known about how to use it correctly."

At the January 26, 1973 meeting of the OB-Gyn Advisory Committee the use of DES and other estrogens for post-coital contraception was again brought up and the Committee was again asked whether the post-coital use of DES could be approved on the basis of available information for its safety and efficacy. A panel of experts had been invited to present their experience to the Committee and representatives of consumers groups were also given the opportunity to present their views. Formal presentations by Dr. R. Blye of NICHD, on the results of the survey of clinical investigations with post-coital administration of DES or other estrogens, of Dr. M. Lipsett, NICHD, dealing with the safety aspects of estrogen usuage, a report by Dr. Lucille Kuchera of the Michigan University Health Service on her own studies with DES, and discussions by Dr. A. Herbst and Dr. D. Proskancer of Massachusetts General Hospital, as well as written comments by Dr. Roy Hertz (by invitation), and letters from Dr. Ralph B. Woolf, Planned Parenthood World Population and from Dr. Philip Corfman, NICH, consultant member of the Committee who was absent, provided the material or deliberations by the seven Committee members present.

It was the unanimous conclusion of the Committee members that there exists now substantial evidence for the effectivity of DES in preventing conception by the post-coital administration of 50 mg. (2x25 mg.) daily for five consecutive days initiated within 72 hours after exposure. It was also the unanimous opinion of the Committee that for this regimen and dosage there is no evidence for a significant risk to the patient, except for some immediate minor side reactions, and that a carcinogenic potential from this dosage has not been proven.

However, because the possibility of a harmful effect on the fetus either from a pregnancy existing at the time of treatment from a previous exposure or resulting from a patient failure during treatment, an early abortion induced by conventional means should be seriously considered even though an action of this kind on the fetus is not known to exist.

On the strength of these conclusions the motion was made and passed, to recommend to the Commissioner approval for the use of DES post-coitally as a contraceptive under the outlined conditions and circumstances, with the provision that this usage is to be considered as an emergency treatment only and that it should not be considered as a method for birth control with continuous and frequently repeated therapy.

A revision of the labeling of DES for use as a post-coital contraceptive is currently underway.

This drug is just one example of a number of complex questions which face the agency and its advisors in the course of drug research and development. The difficult benefit risk judgments are well illustrated by this drug.

Summary

Mr. Chairman, our system to assure patient protection is as carefully formulated as we know how to make it. It is unique in the world since no nation has our IND system and none requires similar institutional or Federal review of drug research involving humans. However, it is not perfect and cannot guarantee complete safety in drug experimentation, nor is there any practical system which man can develop which is likely to do so.

One of the very real difficulties with our system is that it is impossible for the government to monitor all research being conducted in this country. At any one time in this country there are approximately 4,000 active drug investigations going on involving at least 10,000 investigators and tens of thousands of patients in several thousand locations in this country.

It is not surprising that there are, and have been in the past, instances where individual investigators have been found who have not complied with all the requirements laid down in this area or where there have been delays in submission of required information. When we learn of such instances, they are thoroughly investigated and appropriate action is taken, including, if warranted, criminal prosecution of the individual involved. We are carrying on a sampling of investigations to uncover possible problems and have required peer review mechanisms to be set up to provide an independent on-sight mechanism to help assure the rights of patients and the conduct of ethical investigations.

Given the nature of drug investigation, there will always be instances where new toxicity possibilities become known only after humans have already been exposed to a drug. There is no way to avoid this completely and still develop useful drugs. Fortunately, this is a rare occurrence and to the best of our knowledge has occurred only a handful of times out of over 9,000 investigations over the last 10 years. When it occurs, we require the drug sponsor either to do further studies, to modify or terminate his studies as appropriate and to notify the investigators promptly. When indicated, patient follow-up is required of the drug sponsor.

We and others have learned, however, that there are many instances and many reasons why patient follow-up may be impossible to achieve. The difficulties in this area are well exemplified in a report we recently received from a committee of the Drug Research Board of the National Academy of Sciences.

The committee was asked, "With whom should responsibility rest for follow-up of patients who are involved in clinical studies of drugs?". Their answer is as follows:

> "The responsibility for following patients, whatever arrangements are involved, must rest with the investigator. The expenses involved in such follow-up must be provided by the sponsor. The realities of the situation are that long-term follow-up of many patients offers extraordinary difficulties except in certain clinics in the United States. These difficulties stem in part from the extraordinary mobility that exists in this country and in part from the unwillingness or disinclination of many persons to respond to questionnaires or to re-appear for examinations. The fact that government may be involved

> in the follow-up of these patients does not materially affect the issue of practical difficulty in follow-up. In the view of the Ad Hoc Committee, the problem is, for practical purposes, insoluble except under circumstances that world involve intolerable invasions of human privacy."

Nevertheless, the attempt is required though it is frequently unsuccessful.

Some have suggested that our requirements for pre-clinical toxicity testing should be made even more rigid. We have consulted with experts in this area and have concluded that such a step would not be productive at this time or on balance be beneficial to the public. Our current requirements are already the most stringent which exist in any nation and in general increasingly serve as a model throughout the world. Despite this, five months ago, in conjunction with expert advisors, we initiated a complete review of our requirements to see what modifications might be appropriate.

In summary, Mr. Chairman, though it is true that this Nation's concern and system of safeguards for human experimentation are the most extensive in the world, we still have unresolved problems in this area. A great deal of effort is underway to improve this system and public understanding of the complex problems through education and hearings such as this will help resolve some of these problems. We would be pleased to answer any

Senator KENNEDY. At this point in the record, I order printed the "National Advisory Commission on Health Science and Society Resolution" introduced by Senator Mondale and others.

[The text of S.J. Res. 71 follows:]

93d CONGRESS
1st Session

S. J. RES. 71

IN THE SENATE OF THE UNITED STATES

March 6, 1973

Mr. Mondale (for himself, Mr. Bayh, Mr. Brooke, Mr. Case, Mr. Cranston, Mr. Hart, Mr. Hughes, Mr. Humphrey, Mr. Javits, Mr. Kennedy, Mr. McGee, Mr. McGovern, Mr. Moss, Mr. Nelson, Mr. Pell, Mr. Randolph, Mr. Schweiker, Mr. Stevenson, and Mr. Williams) introduced the following joint resolution; which was read twice and referred to the Committee on Labor and Public Welfare

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JOINT RESOLUTION

To provide for a study and evaluation of the ethical, social, and legal implications of advances in biomedical research and technology.

Resolved by the Senate and House of Representatives of the United States of America in Congress assembled, That this joint resolution may be cited as the "National Advisory Commission on Health Science and Society Resolution".

ESTABLISHMENT OF COMMISSION

Sec. 2. There is hereby established a National Advisory Commission on Health Science and Society (hereinafter referred to as the "Commission").

II

MEMBERSHIP

SEC. 3. (a) The Commission shall be composed of fifteen members to be appointed by the President from the general public and from individuals in the fields of medicine, law, theology, biological science, physical science, social science, philosophy, humanities, health administration, government, and public affairs.

(b) Any vacancy in the Commission shall not affect its powers.

(c) The President shall designate one of the members to serve as Chairman and one to serve as Vice Chairman of the Commission.

(d) Eight members of the Commission shall constitute a quorum.

DUTIES OF THE COMMISSION

SEC. 4. (a) The Commission shall undertake a comprehensive investigation and study of the ethical, social, and legal implications of advances in biomedical research and technology, which shall include, without being limited to—

(1) analysis and evaluation of scientific and technological advances in the biomedical sciences, past, current, and projected;

(2) analysis and evaluation of the implications of such advances, both for individuals and for society;

(3) analysis and evaluation of laws, codes, and

principles governing the use of technology in medical practice;

(4) analysis and evaluation through the use of seminars and public hearings and other appropriate means, of public understanding of and attitudes toward such implications; and

(5) analysis and evaluation of implications for public policy of such findings as are made by the Commission with respect to biomedical advances and public attitudes toward such advances.

(b) The Commission shall make maximum feasible use of related investigations and studies conducted by public and private agencies.

(c) The Commission shall transmit to the President and to the Congress one or more interim reports and, not later than two years after the first meeting of the Commission, one final report, containing detailed statements of the findings and conclusions of the Commission, together with its recommendations, including such recommendations for action by public and private bodies and individuals as it deems advisable.

POWERS OF THE COMMISSION

SEC. 5. (a) The Commission or on the authorization of the Commission, any subcommittee or members thereof, may, for the purpose of carrying out the provisions of this joint resolution, hold such hearings, take such testimony, and sit and act at such times and places as the Commission deems advisable. Any member authorized by the Commission may administer oaths or affirmations to witnesses appearing before the Commission, or any subcommittee or members thereof.

(b) Each department, agency, and instrumentality of the executive branch of the Government, including independent agencies, is authorized and directed, to the extent permitted by law, to furnish to the Commission, upon request made by the Chairman or Vice Chairman, such information as the Commission deems necessary to carry out its functions under this joint resolution.

(c) Subject to such rules and regulations as may be adopted by the Commission, the Chairman shall have the power to—

(1) appoint and fix the compensation of an executive director, and such additional staff personnel as he deems necessary, without regard to the provisions of title 5, United States Code, governing appointments in the competitive service, and without regard to the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates, but at rates not in excess of the maximum rate for GS-18 of the General Schedule under section 5332 of such title, and

(2) procure temporary and intermittent services to the same extent as is authorized by section 3109 of title 5, United States Code, but at daily rates for individuals not in excess of the maximum daily rate for GS–18 of the General Schedule under section 5332 of such title.

(d) The Commission is authorized to enter into contracts with Federal or State agencies, private firms, institutions, and individuals for the conduct of research or surveys, the preparation of reports, and other activities necessary to the discharge of its duties.

COMPENSATION OF MEMBERS

SEC. 6. Members of the Commission (other than members who are officers or employees of the Federal Government) shall receive compensation for each day they are engaged in the performance of their duties as members of the Commission at the rate prescribed for positions at level II of the executive pay schedule in section 5313 of title 5, United States Code. Members of the Commission who are officers or employees of the Federal Government shall receive no additional pay on account of their services on the Commission. All members of the Commission shall be entitled to reimbursement for travel, subsistence, and other necessary expenses incurred by them in the performance of their duties as members of the Commission.

APPROPRIATIONS AUTHORIZED

SEC. 7. For the purpose of carrying out this joint resolution, there are authorized to be appropriated such sums as may be necessary, but not to exceed $1,000,000 for each of the two years during which the Commission shall serve.

TERMINATION

SEC. 8. On the ninetieth day after the date of submission of its final report to the President and the Congress, the Commission shall cease to exist.

Senator KENNEDY. Thank you very much.

The first panel this morning consists of Anna Burgess, Monterey, Tenn.; Marcia Greenberger, Center for Law and Social Policy, Washington, D.C.; and Nathan Kase, Yale University School of Medicine.

Miss Burgess is a participant in one of the programs we are exploring this morning. She will be able to offer some significant testimony.

Marsha Greenberger is from the Center for Law and Social Policy in Washington, and recently traveled to Tennessee to investigate the way Depo-Provera is being used. Dr. Kane is chairman of the obstetrics and gynecology department at the Yale Medical School. He too, went to Tennessee to study the patterns of practice with Depo-Provera.

We want to welcome you very much. You are among friends, and we are looking forward to hearing from you this morning.

We want to thank you very much for coming, Marsha. Do you want to lead off?

STATEMENT OF ANNA BURGESS, MONTEREY, TENN.; MARCIA GREENBERGER, CENTER FOR LAW AND SOCIAL POLICY, WASHINGTON, D.C.; AND NATHAN KASE, M.D., YALE UNIVERSITY SCHOOL OF MEDICINE, A PANEL

Ms. GREENBERGER. On January 18, 1973, Dr. Nathan Kase and I went to Cumberland County, Tenn. We spoke with five women who had received the injection of a drug given to prevent pregnancy, and a sixth who had been advised of its availability. All of the women went to the Family Planning Clinic of the Cumberland County Health Department for advice and help with birth control. From their descriptions, it seemed that the drug was Depo-Provera, manufactured by Upjohn Company.

At the time that the interviews were conducted, we did not know whether these women were receiving the drug as part of an investigation approved by FDA, or whether the drug was being prescribed by a physician acting under his authority with or without the knowledge of Upjohn. However, we attempted to determine whether these women received the drug under conditions which would meet the professional standards established by the FDA for approved investigations, and it is my conclusion that these women did not for the following reasons:

(1) The informed consent of these women was not obtained before the drug was administered. None of the women were told that FDA has not approved Depo-Provera for use as a contraceptive. In addition, all of the dangers and risks involved with the drug's use were not fully discussed. Finally, the women were not given adequate explanation of the alternative methods of birth control which were available.

We showed the women a consent form sent by Upjohn to its investigators concerning Depo-Provera for contraception. None had seen the form before. In addition, they said that they saw nothing resembling the form, and did not remember signing any form concerning Depo-Provera at all.

(2) In at least one case, the consent to receive the drug was not freely given. Anna Burgess, who is here today, will relate her experiences with Depo-Provera. It is my belief that she did not exercise a free choice when she consented to receive the drug. There were hints of coercion in a second case as well. This woman was visited repeatedly by nurses from the Family Planning Clinic until she agreed to follow their advice and use Depo-Provera for contraception.

(3) Several of the women had medical problems after taking the drug, but had not been warned that such side-effects might occur. Three of the women became extremely nervous and irritable, and two also had headaches and backaches. These three women were so bothered by their nervous state that they went to their private doctors, rather than return to the Family Planning Clinic, for help. The first women eventually had a tubal ligation; the second was given an injection to neutralize the effects of Depo-Provera, and then had heavy bleeding, dizziness and backaches; the third bled profusely and was hospitalized four times, finally for a tubal ligation.

The last two women reported no serious problems after taking Depo-Provera. One had a weight gain, skin problems and eye aches, but she was content to continue taking the drug even after we discussed the warnings contained in the consent form. The other had no problems with the drug except a gain in weight. She was concerned about taking Depo-Provera once she learned of the risks involved, but was coufused as to who she could go to for advice about the best method of birth control for her particular situation.

(4) Medical treatment, supervision and follow-up given these women seemed to be inadequate. Dr. Kase will deal with these issues. Dr. Kase, do you want to discuss them now?

Dr. KASE. I will wait.

Ms. GREENBERGER. Perhaps at this point it might be best if Ms. Burgess would describe her experiences with the drug.

Ms. BURGESS. In July of 1971, I was called into the welfare office. The welfare lady asked me if I had signed up on family planning.

Senator KENNEDY. Would you pull the microphone closer to you. You have come a long way. What would be terribly interesting, if you felt comfortable, is for you to tell us a little bit about how you came to take Depo-Provera. Just in your own words, if you felt you could, tell us about visiting the clinic and what happened there.

Ms. BURGESS. Do you want me to tell it in my own words?

Senator KENNEDY. We will put all of this into the record. Maybe you could tell us something about yourself.

Ms. BURGESS. My name is Anna Burgess. I was born September 11, 1951. I live in a three room house. We have no running water, no electricity.

[Background statement of Ms. Burgess follows:]

BIOGRAPHY

My name is Anna Burgess. I was born September 11, 1951. I've lived in a community near Crossville all my life. I live in a three room house with my mother, two brothers and my 21 month old son, Roger. We have no running water or electricity. We light with a kerosene lamp and cook and heat with a wood stove. Before we had a well drilled, three months ago, we hauled water from a stream. The only income we live from is my welfare check ($99) and the commodities.

I went to the seventh grade. When I was five years old I got crippled up. The doctor suggested complete bed rest for a year. I didn't get better, so my mother took me to different doctors and they sent me to Knoxville. After three or four months, they said I had infection of the bone. I stayed there about 11 months altogether the first time. I had five operations. The last one was in 1963.

Ms. BURGESS. In July of 1971, I was called to the welfare office. The welfare lady asked me if I had signed up for family planning. I was not on it then, and she said I ought to be taking something or other. She said they'd rather feed one youngun as two. She made arrangements for me to go to the health department. She said the shot would be the best because I wouldn't have to worry about forgetting it. She said it would last 6–8 months. I didn't go the first two times she arranged it because I was scared a little. In August or September one, I went to family planning at the health department. I signed up with them, that's all I ever signed. I sat and waited a while, and they called me into a back room. They weighed me, took my blood pressure and asked about my blood. They didn't take any blood because my baby wasn't three months old yet. I went out front and waited a few minutes and they called me back into another room. A nurse who I don't know told me to take my clothes off and put a paper gown on. They asked if I'd had a Pap smear. I said no. The doctor took one. He also checked my chest with a stethescope. Then he told me to turn on my left side and gave me the shot. My hip hurt for two weeks. The next month I started spotting for about 3 days. They had told me I would have no period for 6–8 months. I started getting nervous, not acting like myself. I went to a private doctor. He didn't know nothing about the shot. He called the health department and then he gave me a shot to start my period, but he said he didn't know if it'd work. About a week later my period started. It lasted three to four weeks. I passed about a pound of flesh. The welfare called me in for another interview and asked how the shot was working. I told them everything that had happened. They suggested I go back to the health department and get the coil or pills. I went to the health department after I got two letters. My blood was low, so they gave tonic. This happened twice. I didn't take all the tonic. After that, I got tired of messing with them and went to a private doctor.

Senator KENNEDY. You took the drug. Did the doctors tell you at any time that it was an experimental drug?

Ms. BURGESS. No, they did not.

Senator KENNEDY. Did the doctors tell you at any time of the potential side-effects of the drug?

Ms. BURGESS. No, they did not. They did not tell me nothing, except the impression it was safe.

Senator KENNEDY. They told you it was perfectly safe?

Ms. BURGESS. Right.

Senator KENNEDY. Do you feel the social workers were pressuring you to take the drug?

Ms. BURGESS. If it had not been for them, I would not have took it. If it had not been for the welfare people, I would not have taken the stuff in the first place.

Senator KENNEDY. Why do you feel they wanted you to take the drug?

Ms. BURGESS. To keep from having another child.

Senator KENNEDY. The welfare people wanted what?

Ms. BURGESS. They wanted me to take the birth control shot so there would not be no more children.

Senator KENNEDY. They were urging you to take it so you would not have any more children?

Ms. BURGESS. Right.

Senator KENNEDY. And you felt that you should take it because of their suggestion.

Ms. BURGESS. Well, it seemed the way I took it was, I thought they would take the check or something.

Senator KENNEDY. I am sorry, I did not hear you?

Ms. BURGESS. From the impression I got, if I did not take birth control, they would take the check.

Senator KENNEDY. If you did not take the Depo-provera they were perhaps going to threaten your assistance program?

Ms. BURGESS. In a way, because they said they would rather pay one child as two.

Senator KENNEDY. Maybe you could tell us again what you feared. If you did not take the drug, what did you think might happen to you?

Ms. BURGESS. I thought they would take my check at that time. At that time I could not work and take care of the baby——

Senator KENNEDY. Take your check away?

Ms. BURGESS. That is what I thought they would do if I did not take the birth control that they suggested.

Senator KENNEDY. They urged you to take it, and they did not indicate to you that it was an experimental drug, that it has any dangerous side-effects?

Ms. BURGESS. They did not.

Senator KENNEDY. Did you consider going to your own doctor or private doctor?

Ms. BURGESS. At the time I did not have the money to go to my own doctor.

Senator KENNEDY. You did not have a doctor?

Ms. BURGESS. I had a doctor, but I did not have the money to go to one.

Senator KENNEDY. You did not have the money to go to your private doctor?

Ms. BURGESS. Right.

Senator KENNEDY. So even though you felt that you wanted to go, and even though you had a doctor, because you did not have the money to go to the doctor, you did not go. Is that right?

Ms. BURGESS. Did not go to the doctor for quite a while after.

Senator KENNEDY. How much would it cost for a doctor's visit?

Ms. BURGESS. Ten or twelve dollars.

Senator KENNEDY. Is that a lot of money?

Ms. BURGESS. It was for us.

Senator KENNEDY. It is for a lot of people.

Did you feel that you were well treated at the family planning center?

Ms. Burgess. Not really.

Senator Kennedy. Would you go back there for any further treatment?

Ms. Burgess. Not for myself, but I took my baby for his health shots.

Senator Kennedy. You would not go for your own health reasons, but you brought the baby back to get some shots, is that right?

Ms. Burgess. That is right.

Senator Kennedy. Would you tell us about the impact the drug had on you?

Ms. Burgess. I could not stand my own self and could not stand to hear the baby cry. If anybody comes in, and company comes in. I would have to walk off and leave them to keep from talking to them.

About a month later I started spotting. Then I went to a private doctor and asked him to give me a shot to start my period, and he said he did not know whether it would work or not, he would call the health department and find out about the shot, because he said he did not know about that.

After that, my period started and I bled for about three or four weeks and passed a half a pound of flesh and still bled for quite a while.

I finally went to my own doctor.

Senator Kennedy. Did I understand you correctly that when you did go to your doctor you mentioned this to him, but he had never heard of the drug?

Ms. Burgess. That is right. He had never heard of it.

Senator Kennedy. Now, if you can just tell me again the effect of the drug on your personality. You felt it made you more nervous?

Ms. Burgess. I was so nervous I couldn't stand nothing.

Senator Kennedy. After you took the drug?

Ms. Burgess. After I took it. I stand around and hear my baby crying—I couldn't stand to hear the baby cry or nothing else.

Senator Kennedy. And before taking the drug——

Ms. Burgess. I didn't have no trouble at all.

Senator Kennedy. And after you had the drug?

Ms. Burgess. I was real nervous and couldn't stand myself and nobody else hardly.

Senator Kennedy. Are you glad you took the drug?

Ms. Burgess. No.

Senator Kennedy. Is it difficult for you and your friends to see doctors where you live?

Ms. Burgess. No. I have got medicaid now, and from the welfare, and I could see a doctor, as my friends and all, we go see the doctor whenever they need to. No problem.

Senator Kennedy. We will listen now to Dr. Kase; we might have a few more questions after he concludes.

STATEMENT OF NATHAN KASE, M.D., CHAIRMAN OF DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN, CONN.

Dr. Kase. Mr. Chairman and members of the committee, I would like to describe my observations derived strictly from interviews with six patients receiving the drug in Cumberland County. I will make some suggestions for repair of the difficulties I observed.

1. An injectable contraceptive drug, presumably Depo-Provera, was prescribed in this county and used in the practice of medicine not as an experimental drug. Informed consent was not obtained, nor was an attempt made to achieve patient awareness or acceptance of this issue. In particular, the potential short and long term hazards of the drug were not discussed in any instance studied.

2. On the basis of the patients' description of events, the routine safeguards, consistent with good medical practice, which should be applied prior to initiating any therapy, were not offered to these patients. Adequate overall care prior to, during or subsequent to usage was not regularly, predictably or responsibly available or achieved.

3. At least one patient studied appears to have been coerced or felt coerced by her welfare agency to accept a birth control medication, preferably Depo-Provera, because of its ease and certainty of effectiveness.

4. According to a brochure describing birth control possibilities available for distribution to all clients of the Cumberland County Family Planning Clinic, long term injectable birth control is described as experimental and not utilized.

5. Although the full range of approved birth control measures appear to be available to these clients, from the patients' description of events it appears that the agency in question regarded institution of contraception in any form as its primary objective. Little, if any, effort was expanded to achieve individualized methodology application to optimize acceptance or to cultivate enthusiastic, confident patient usage.

As a result, local folkways—that is, pronounced fear of the IUD—remained unchallenged by any educational initiative by responsible authorities. As a result, options short of sterilization were limited and "escalation" to the experimental injection quickly gained popular interest and use.

6. Professional "feuding" between local physicians and family planning authorities has led to contradiction and confusion among the patients in this county. Lack of unity, sometimes taking the form of unethical pronouncements by medical people in the area has fostered distrust and indecision amongst patients.

Senator KENNEDY. Do you wish to amplify on that, Doctor?

Dr. KASE. If we pursued this part of the patient's testimony we would have found examples: What have you done to yourself? Why did they let you take that shot? I gathered from the interviewees that there was physician concern for their patients, but also a concern for medical priorities that individual physicians sought to assert in this county.

Senator KENNEDY. What do you mean by that?

Dr. KASE. I think that there was an element of intrusion on the physicians in the county by the health department clinic, and that led to reactions in the form of anxiety-producing comments which pervade all of these interviews. Patients related anxiety that could have only come from the physician provocation.

Senator KENNEDY. Let me expand on that. What sort of anxiety?

Dr. KASE. No; medical anxiety; physical damage; potential unstipulated side effects.

The alternatives offered were sterilization or classic medications that had not worked or were not used properly because of poor education and direction by all physicians.

Senator KENNEDY. You mean they offered either sterilization or this or that drug?

Dr. KASE. There were very limited alternatives, either IUD or sterilization, based upon my observations of the six interviewees.

Senator KENNEDY. Are these valid alternatives?

Dr. KASE. The alternatives should be multiple. The important thing is the patient has to be informed to make an individualized choice. That was not accomplished by either authority in this community.

Ms. GREENBERGER. If I may interrupt for a moment to illustrate the point Dr. Kase was making, in one case a woman was visited by the public health department nurses and told she should receive injections of Depo-Provera. One nurse told her to go to a private physician and get a general prescription allowing her to receive a birth control device. She was to bring the prescription to the clinic and then she would receive the injection.

The patient responded to the nurses that her doctor did not take kindly to the public family planning clinic, and therefore she did not think he would give her such a prescription. One of the nurses replied that her husband was a physician, and that he would give the woman the prescription that was needed. That is the way in which this woman came to take the injection.

Dr. KASE. Senator, this appears to be a factor in thwarting any possibility of mounting a carefully community-wide family planning effort to aid a most needy and otherwise accepting target population. There was disorganization.

Now, if I may, I have some suggestions and some ideas based upon these interviews.

First of all, as well known to you, the Cumberland County use of Depo-Provera for contraceptive purposes is not an isolated nonapproved use of this drug. As a contraceptive agent or as an agent for control of menstrual irregularity and flow, this drug is widely used in this country, contrary to its narrow approved uses in endometriosis and endometrial carcinoma.

Senator KENNEDY. Dr. Edwards indicated he would have a very deep concern if this practice was widespread. You claim that it is widespread. On what do you base your statement?

Dr. KASE. Direct observation and conversations with colleagues throughout the country.

This drug has been in this nonapproved available limbo for a very long time. I would like to make some suggestions in a moment to limit that prolonged availability.

Senator KENNEDY. Before you do, is it your impression, based upon your study or conversations with colleagues, that it is usually the poor and the uneducated who are most likely to be victims of these experimental therapies?

Dr. KASE. No; not exclusively, surely.

Senator KENNEDY. I did not say exclusively.

Dr. KASE. The majority of patients are patients who choose a nonmechanical, non-scheduled contraceptive method.

Senator KENNEDY. What group of our population use these methods?

Dr. KASE. The uneducated and the poor.

Senator KENNEDY. Then let us go back to the previous question. Would you say that they are more likely to be given the experimental therapies than others in our population?

Dr. KASE. They are likely to choose it, sir. In most instances they are not likely to be given it as primary medication.

Senator KENNEDY. Why are they most likely to choose it? Is that the most comfortable method? Is it the safest?

Dr. KASE. I think it is neither the most comfortable nor the safest, but it is easier.

Senator KENNEDY. Easier for whom?

Dr. KASE. For the patient in terms of administration. A single injection every three months is an appealing element to this drug, and it is very effective, though not entirely effective.

It surely is a tertiary drug in contraception, well below the intrauterine device.

Then if I may enlarge on that point, the particular patient population that might use Depo-Provera is generally given birth control advice and direction in county facilities such as this, populated by physicians, generally volunteers, who spend long hours seeing large numbers of patients.

As the hours and patients mount, the degree of individualized care that is given does decrease, so the chances of unprepared side-effects—the patient is uneducated, unprepared for those—leads to the escalation of the side effects and need for different medications.

Senator KENNEDY. Why are there not more health personnel out in those communities?

Dr. KASE. That is the difficulty with the entire structure and organization of both our profession as well as how we educate these professionals.

Senator KENNEDY. Is it one of financing, too?

Dr. KASE. Financing is a part of the issue. I think it has been an obsession for some. It is not the exclusive issue.

The cost of care is important, but there are elements to getting the kind of person to offer care and so forth.

If I may proceed, I would like to offer some suggestions to relieve this problem.

Senator KENNEDY. Yes.

Dr. KASE. I think this nonapproved use arises from several factors, including:

The dosage range for an approved indication is similar to nonapproved or experimental applications.

The results of experimental uses are excellent and widely publicized by physician-investigators in professional journals, lay press, professional meetings.

Until very recently, October, 1972, package inserts and other physician guidelines—such as the PDR—did not indicate which uses of the drug were experimental and nonapproved.

Senator NELSON. I did not understand that. Are you saying not until October, 1972 did the package insert give the indications for use?

Dr. Kase. No; gave the instances wherein the drug was used for experimental purposes, and not to be used for general use. Only in the most recent, in October, 1972, was that package insert addition made.

Senator Nelson. The package insert has always stated what the approved indications were for its use; is that right?

Dr. Kase. Right.

Senator Nelson. Then you say in October 1972 what was added?

Dr. Kase. They added the nonapproved use; what should not be—this drug should not be applied in this instance, and as a contraceptive drug.

Senator Nelson. Why was that done?

Dr. Kase. I would not care to comment. I do not know the complete explanation, and I would not offer part of it.

Senator Nelson. This was an additional requirement by the Food and Drug Administration, I take it?

Dr. Kase. I have the insert with me, sir. If I may—if this answers your question.

Under Warnings it says: Item No. 3. Use of Depo-Provera for contraception is under investigation. Since there are unresolved questions relating to its safety, for purposes of contraception this is not an approved indication for its use.

I was mentioning a lack of distribution control so, to return to my statement, apparent lack of availability restrictions and distribution control by manufacturers, distributors, and pharmacists allow excess, nonapproved usage to go unmonitored.

The persisting and unfilled demand for a "perfect" contraceptive, applicable and acceptable to a large segment of our population that is poor, uneducated, intimidated by authority or disdainful of that authority, has led to use of nonapproved techniques where the appeal of effectiveness takes precedence over insured safety implicit in FDA approval.

Even in patients competent to perceive options and develop their personal priorities regarding effectiveness and safety these judgments are modified or reversed when issues such as family size, poverty, sexuality, sterility and abortion supervene. Even after reading the Depo-Provera consent form which describes the possibility of cancer, long term infertility and the like, one patient surveyed, who knew she had a breast problem, and who did want more children but whose husband does not work, chose to continue on this medication.

Suggestions to avoid future experimental drug misuse and reduce approved drug abuse:

1. Review FDA procedures controlling clinical trials, particularly in mechanisms for limitation of distribution and availability of experimental drugs approved for one use but not approved for another;
2. Package inserts concerning drugs approved for some use but experimental for other uses should clearly stipulate these restrictions.

As I have noted, this just became available in Depo-Provera in 1972, in October of 1972. I have no idea whether this applies to all drugs.

3. Commercially produced and widely used references (such as the PDR) should follow the same (as in 2 above) stipulations, citing both approved and still experimental uses for a particular drug.

4. Based on phase II testing results, phase III consent forms should be drug specific and the consent obtained should be in written form.

My fourth suggestion: A package insert should be required for patient use and information for all prescription drugs clearly stating the indications, contraindications, hazards and usual dosage. This will enable some degree of patient edification and consent prior to purchase or use of any drug. I appeal that it be written in layman's language. The FDA inserts are difficult. Doctors do not tend to read them thoroughly.

My fifth suggestion: Wherever possible medications should be packaged in the quantities accepted by authoritative medical management procedures rather than in arbitrary volumes or numbers. This will insure proper dosage and duration of most common therapies.

Because Depo-Provera was prolonged in its phase III testing, and availability came through the back door, may I suggest that the FDA combined with knowledgeable representatives from industry and the profession should initiate prospective, continued drug testing studies in questionable areas uncovered during phase studies and toxicology *after* approval. Presumably, this could shorten drug approval time, diminish nonapproval use, but provide continuous, well-controlled, more easily monitored drug surveillance.

Finally, although these suggestions undoubtedly would diminish the problem associated with general drug use in this country, in my opinion, they are peripheral to the basic issue at hand, that is, the rapidly deteriorating quality of the interaction between patient and his or her physician.

Careful evaluation of the organization and structure of medical care, by the profession, as well as by public and private resources, is essential. In addition to the concern over the cost of care, attention must be paid to the quality, distribution and the types of professionals involved in medical care systems.

I might add that as a professional, not just as an academician, the Federal budget proposal would only increase the difficulties of which Depo-Provera is only the tip of the iceberg. It will in many ways make our problems and our patients' problems far worse.

If you wish, I would like to expand upon that question.

Senator KENNEDY. You talk about these declining relationships between the doctor and the patient. Why are are they important, and why are they declining?

Dr. KASE. Why is it declining? I am not sure I can cite all the reasons. I do not know that I know them or that anyone knows them.

I think that part of the issue is that there are not enough health professionals available. There are, furthermore, within the health professions limited access and replenishment of knowledge, so that physicians are increasingly threatened as new information appears and as they get further behind.

The attention to cost, the involvement in the financial sphere of an otherwise professional relationship I think clouds the issue. Money has become a factor in how much time, how available the physician is, when he is available, and under what circumstances.

I think there has been a preoccupation furthermore with just churning—I mean just churning—out large numbers of quickly trained up-to-the-minute physicians, but for next minute their education falls short of need.

We need a very general reappraisal, if I might suggest, of the kinds of educated people we accept into the health profession. I can see fewer physicians and more health professionals of assistant and physician associate level.

At our school we are seriously considering a nondoctorate degree for a health professional, an individual who comes from a community, who lives and remains in that community, who is employed and not "voluntary." It may be that his whole professional object will be restricted to offering contraceptive care and family planning.

Senator KENNEDY. Doctor, to what extent are experimental drugs commonly used?

Dr. KASE. It is very limited. I think we have heard of two examples where there has been excessive use today.

Senator KENNEDY. You call it excessive use.

Dr. KASE. Thank you for correcting me. I would say "experimental use." In both instances there are specific uses.

Senator KENNEDY. You said "widespread use" before of Depo-Provera.

Dr. KASE. I think "widespread" implies just distribution. "Excess" implies poor use. However, I meant it in that context.

I think drugs are made available in the manner that Depo-Provera is and as a result used very widely. However, I think when one considers the total therapeutics of this Nation, this is a small matter. However, it is not insignificant to the patient who receives the drugs, surely Finally, there are sufficient abuses in approved drugs.

Senator KENNEDY. Marcia, we interrupted your testimony to let the others present testify. Would you like to continue your statement, and conclude it? Then we will come back.

Ms. GREENBERGER. Fine. I had some additional information as to the use of Depo-Provera for contraceptive purposes aside from the interviews that Dr. Kase and I had with the women in Cumberland County, Tenn.

I learned that Arlington Hospital and School, which I understand is a facility of the State of Tennessee for the mentally retarded near Memphis, is also prescribing Depo-Provera for contraception. The information that I have concerning the use of the drug in this institution is mainly based upon a telephone conversation that I had on January 31, 1973, with Dr. Edward Mogan, a physican associated with Arlington. Dr. Mogan stated that Arlington began to give Depo-Provera to women of childbearing age in 1969, and continues to do so at the present time. He said that 250 female residents are receiving the drug, and that it is being given with two purposes in mind—contraception and the prevention of menstruation.

I mentioned to Dr. Mogan that it was my understanding that Depo-Provera was not approved by FDA for use as a contraceptive. Dr. Mogan thought that I was mistaken and explained that Arlington had no trouble in obtaining the drug. He added that many private physicians in that part of Tennessee were prescribing the drug for birth control and that Memphis and Shelby County Public Health Departments were using it as a supplement to the pill.

I believe that it should be determined whether the female residents of Arlington received Depo-Provera under conditions which would have been approved by FDA:

(1) Was informed and voluntary consent given by the legal guardians of the female residents or of the women themselves? According to Dr. Mogan, in the first year all of the guardians were told of the drug's proposed use and most signed consent forms. After the first year, Arlington discontinued the requirement of signed consent forms but discussion groups are still held to inform the guardians of the use of the drug.

Dr. Mogan said that the majority of residents at Arlington are indigent. Given the lack of options available to the poor, it should be determined whether the guardians felt free to refuse permission for the use of the drug. It should also be determined whether the guardians knew of the drug's experimental status and the risks involved in its use. Finally, it should be determined whether less drastic alternatives were presented to the guardians to consider.

(2) I wonder whether the female residents were given adequate medical treatment, supervision, and followup? Dr. Mogan said that the medical followup given these women is not of the standard usually found in a university, but he feels that the drug has been prescribed successfully during the last 4 years with no serious problems.

Dr. Mogan said that before Arlington began to use Depo-Provera, consultations were held with Dr. Stewart Fish of the department of obstetrics and gynecology at the University of Tennessee School of Medicine, and with Dr. Leonard Brooks, who was the family planning clinic physician for five counties near Arlington.

On January 31, 1973, I spoke with Dr. Fish by telephone and he confirmed that he had recommended that Arlington use Depo-Provera. He added that the drug is not used in the family planning clinic of the University of Tennessee, but that under certain relatively infrequent circumstances, it is given in the University of Tennessee Hospital as a birth control device.

On February 5, 1973, I spoke to Dr. Leonard Brooks by telephone. He left Tennessee this past September and is now located in Washington, D.C. Dr. Brooks stated that he had advised Arlington to use Depo-Provera. In addition, in his capacity as the family planning clinic physician for five counties in Tennessee, he prescribed the drug to many women for the purpose of birth control. He said that the Tennessee Public Health Department has a computer printout sheet indicating that between 1,000 and 1,500 women are given Depo-Provera each year in the State.

Finally, Dr. Brooks said that during the period that he was in Tennessee, he approached Upjohn about becoming an investigator of the use of Depo-Provera for contraception. He was refused, on the grounds that the company did not want to incur the extra expense of an additional investigation of the drug.

Given what appears to be the widespread use of Depo-Provera for contraception in Tennessee outside of FDA approved investigations, a series of troubling issues arise.

1. Is Depo-Provera prescribed in Tennessee according to sound medical practice? There are broad questions about the quality of care given these women, and the health care which is generally provided to the poor and to those who are institutionalized. I believe that Dr. Kase will address this issue.

2. Does Upjohn have any legal responsibility for the widespread use of Depo-Provera for contraception in Tennessee? If Depo-Provera were a totally new drug with no approved uses, Upjohn would have clear responsibilities regarding its use. However, Depo-Provera is an approved drug with nonapproved uses. When this type of drug is at issue, it appears that:

a. Upjohn need not always label the drug with warnings of its investigational use.

b. Upjohn need not record the uses to which the drug is put outside of its own investigations.

c. Upjohn may commercially market Depo-Provera for contraception.

FDA has proposed regulations dealing with approved drugs that have nonapproved uses. The effect of these regulations upon Upjohn should be determined.

3. Does the law provide sanctions against the Tennessee physicians who prescribe Depo-Provera for contraception? The major legal remedy against physicians available to injured patients is the malpractice suit. This remedy will not help most of the women I spoke with in Tennessee:

a. The patients must know that such a remedy exists.

b. Lawyers must be available to represent the patient, but lawyers are often scarce in rural and poor areas.

c. Generally, the patients must be able to pay the attorneys. Poor people cannot afford lawyers' fees, and a contingency fee arrangement is rarely possible. A poor person who is injured often cannot show substantial monetary injury in the form of lost wages and the like—a problem which is especially acute for women.

d. Courtroom litigation requires making public very private problems. Many of the women would be reluctant to publicize their injuries, for fear of official reprisals and out of a sense of modesty.

4. What other safeguards are needed to adequately protect the public with regard to the use of new drugs?

It is essential that a drug's nonapproved uses be clearly stated in all drug inserts and advertisements. Therefore, drug manufacturers should be required to attach labels to each drug shipment warning of the drug's investigational uses.

In addition, drug manufacturers should have a duty to maintain detailed records of drugs with nonapproved uses so that possible misuses could be detected.

Finally, patients should be fully informed of the risks involved in suggested treatment as a general matter, but especially where nonapproved drugs are involved. Therefore, drug manufacturers should be required to provide package inserts warning of the risks involved in use, to be given to all patients receiving the drug. Also, FDA should have the jurisdiction to require physicians to discuss such warning with the patient, and give the patient the insert when the drug prescribed is not packaged, but given in the form of an injection.

Senator KENNEDY. How do you know what Upjohn has provided?

Ms. GREENBERGER. It is my understanding that Upjohn is the only manufacturer of Depo-Provera.

In addition, I had gotten the sense from Dr. Brooks that Upjohn was the manufacturer which was providing the drug in Tennessee.

I certainly do not have any indication from Upjohn themselves that they were providing it.

Finally, I have seen copies of consent forms which are prepared by Upjohn for investigations of the drug, and I know that they are certainly manufacturing it. That seems to be clear.

Senator KENNEDY. Have you made a review of the different consent forms provided by Upjohn and the Arlington Hospital? Have you seen those two forms?

Ms. GREENBERGER. I have seen two revised forms that Upjohn apparently provides to investigators to give to women who receive the drug for contraceptive purposes.

Apparently recently the form was revised and contains more stringent warnings about the possibility of cancer. Aside from that there are fairly extensive warnings about possible sterility, and that sort of thing.

Senator KENNEDY. We will put those in the record, but, as I understand it, the Upjohn study has three pages of consent form, and the Arlington Hospital and School form is one page. I would like these to be included in the record.

[The consent forms referred to follow:]

REVISED DEPO-PROVERA WRITTEN INFORMED CONSENT FORM FOR CONTRACEPTIVE STUDIES

IMPORTANT NOTE: This is NOT the same informed consent form that you signed before. It has been changed to bring to your attention that breast cancers have developed in some beagle dogs undergoing long-term tests with injections of Depo-Provera. Please read it carefully.

This is to certify that I, ______________________________, hereby agree and consent to receive an experimental drug called Depo-Provera every three months under the care and supervision of Dr. ______________________________. I understand that this injection will be given to me in an attempt to keep me from becoming pregnant. I have been told that tests in dogs injected with this drug showed that some of them developed tumors in their breasts. Some of these tumors were cancer and spread to other organs. It is not known whether or not similar tumors or cancers will grow in my breasts after receiving the drug.

It has been explained to me that there are available other non-experimental methods of preventing pregnancy such as pills, vaginal creams, jellies, foams, diaphragms, various devices which are inserted into my womb and use of a rubber (condom) by my husband. The effectiveness of these various methods of contraception, as well as the advantages and disadvantages of each method, has been explained to me. Surgical sterilization of myself or my husband (along with its risks, advantages and disadvantages) has been explained to me as a nonreversible method of contraception. I have also been told of the effectiveness of Depo-Provera.

I have read and understand the pamphlet prepared by the American Medical Association, American College of Obstetricians and Gynecologists and the Food and Drug Administration informing users of the pill about the possible problems which a woman may encounter during its use. I understand also that Depo-Provera is similar to the pill in that I may have some of the same problems occurring that are mentioned in the pamphlet such as blood clots, tender breasts, nausea, vomiting, weight gain, weight loss, spotty darkening of the skin of the face, mental depression, elevated levels of sugar and fatty substances in the blood, dizziness, loss of hair, increase in body hair and increased or decreased sex drive.

It has been explained to me that it is quite likely that I will have unexpected vaginal bleeding, completely irregular menstrual cycles or no menstrual bleeding at all as a result of the Depo-Provera injections. I also understand that the injections may have some effect on the amount of estrogenic and adrenal hormones produced in my body and that the importance of these changes is still being investigated.

I understand, also, that after a woman stops taking Depo-Provera there may be an unpredictable and prolonged delay before she is able to become pregnant or may be unable to become pregnant at all. Because of the possibility of an occasional case of permanent sterility, Depo-Provera should not be used by women who may wish to have another baby in the future.

I have tried all other kinds of birth control methods and cannot use them or I refuse to use all other kinds of birth control methods. Therefore, I hereby volunteer of my own free will to receive injections of the experimental birth control drug, Depo-Provera, with the full knowledge and understanding that it produced breast tumors and cancer in some dogs and it is not known whether similar tumors or cancers will develop in my breasts.

I understand that I may withdraw from this investigational study of the use of Depo-Provera for contraception at any time.

Signed: ______________________ ______________
(Patient) (Date)

Witnessed: ______________________________

(Optional on Part of Investigator)

This is to certify that I, ______________________, husband of ______________________, hereby agree and consent to have my wife receive injections of the experimental drug, Depo-Provera, every three months. It has been explained to me that my wife may not be able to become pregnant after discontinuing Depo-Provera.

Signed: ______________________ ______________
(Patient's Husband) (Date)

Witnessed: ______________________________

ARLINGTON HOSPITAL AND SCHOOL
Arlington, Tennessee

PERMIT FOR DEPO PROVERA PROGRAM

I, ______________________________ (father, mother or legal guardian) of ____, now a resident of Arlington Hospital and School, give my permission to enter her into the program designed at Arlington Hospital and School to use depo provera.

This drug is to be injected every three months for the purposes of preventing menstruation, thereby making resident more comfortable and to lessen nursing care.

A second purpose is that of preventing pregnancy in the event of exposure.

____
PARENT OR LEGAL GUARDIAN

____
RELATIONSHIP

DATE ______________________________

ENM

Ms. GREENBERGER. Right. I just recently saw the consent form from Arlington, I had not seen it before. That is why I questioned in my testimony as to whether during the discussions held with the guardians in Arlington, the dangers involved in the use of the drug were discussed. It certainly does not appear that they were from the consent form.

Senator KENNEDY. Anna did not sign anything like that?

Ms. GREENBERGER. I do not believe that she did. And, none of the other women we spoke to remembered seeing any form even vaguely resembling the form we showed them, and certainly they did not remember signing such a form.

Senator KENNEDY. Let me ask you, Marcia, what her legal rights are. As an attorney, what are Anna's legal rights now that she has participated without informed consent? You are a lawyer advising her.

Ms. GREENBERGER. I have not reviewed Ms. Burgess' case specifically, but there are some general legal principles which apply to this situation. First of all, I assume, as the FDA assumes, that the agency does not have jurisdiction over the use of the drug once it reaches the pharmacy and is prescribed locally. The interstate commerce part of the action stops; and therefore there is no general FDA regulation against such use of the drug.

I have questions as to whether Upjohn has any responsibility for the manner in which the drug was used. Apparently the FDA does not require Upjohn or anyone else to give warnings of the investigational use of the drug to physicians in package inserts or to patients.

Senator KENNEDY. We have heard the testimony of an individual who has taken an experimental drug without her consent. What are her rights?

Ms. GREENBERGER. I would think that her basic right would be the malpractice suit, and that is the essential remedy which the law provides to patients at this point in time who feel they have been injured by negligence in medical practice.

Senator KENNEDY. Does she have a case if she cannot show some kind of injury?

Ms. GREENBERGER. She does not have any case at all.

Senator KENNEDY. So in order to have a case, you really have to be injured by experimental drugs?

Ms. GREENBERGER. You have to be hurt, you have to show the connection between the administration of the drug and the hurt, and you have also the problem of whether or not the drug would be considered generally prescribed for treatment in that area of the country.

I wonder in Tennessee how a judge would interpret that requirement, given the fact that this drug is widely prescribed.

Senator KENNEDY. If she were given an experimental drug which cannot be proven to have done injury to her, she does not have a case, does she?

Ms. GREENBERGER. That is right, she has not.

Senator KENNEDY. She only has a case if she is injured?

Ms. GREENBERGER. That is right. The law requires that some injury be shown. But even in the most perfect of legal situations where the connection between the administration of the drug and the injury can be shown, and it can be proven that the physician was negligent in administering the drug, I still question whether this sort of malpractice remedy provides any sort of safeguard to a woman such as Ms. Burgess, or any other women we spoke to in Tennessee.

I think there are several reasons why the malpractice suit is totally inadequate as a remedy when we are dealing with poor women and poor people generally in the population.

First of all, people must know that they have a right to bring a suit for malpractice. Although I did not mention the possibility to any of the women, and I never asked Ms. Burgess if she knew that she could bring such a suit, I would doubt this woman or the others we spoke to had ever considered the possibility or knew it was an available remedy.

Second, even if they know of the remedy, they have to find a lawyer who will bring suit for them. When you are in a rural area of the county, or in many poor areas, lawyers are hard to come by.

I think this has been especially aggravated by the administration's attitude toward the OEO legal services program. That one basic source of lawyers for poor people is in danger of being eliminated.

Then, even if you can find a lawyer to represent you, there is a problem of how this lawyer will be paid. Most lawyers will require compensation for services they provide. Poor people are rarely able to come up with the fee to cover the services.

A common situation in malpractice suits is for the lawyer to have a contingency fee arrangement. He will collect as his fee a portion of the recovery if the suit is successful. However, with poor people a contingency fee is rare because they cannot show monetary damages which resulted from their injury in the form of lost wages and things of that sort. Therefore, their recovery will be too small to cover the lawyer's fees.

That is especially a problem with women—especially housewives—who rarely receive wages for their services.

Senator KENNEDY. For people who live in rural communities, such as Appalachia?

Ms. GREENBERGER. Right. Poor people who do not have substantial wages, and women generally who are often housewives and unfortunately are not paid for the work that they do have difficulty in recovering substantial monetary damages.

Finally, in a malpractice suit, the very essence of courtroom litigation requires making public very private matters, and it takes a very courageous person to come before a room filled with strangers and bare such personal matters.

Many of the women we spoke to were not willing to make such matters public, were very modest about the problems that they had incurred, and were also very worried about the problem of some sort of repercussion if they publicly complained about the treatment that they received.

As a result it would seem to me that the women in Tennessee just would not be served by the availability of the malpractice suit.

I also come to the conclusion that it is essential that patients, such as the women in Tennessee, be informed of the risk involved in the use of drugs when they are given those drugs. I think that the whole statutory and regulatory scheme should be reviewed with that point in mind.

Is there any impetus on the part of Upjohn, on the part of the private physicians, on the part of the Government, to get the information to patients?

Apparently there just is not at this point. Upjohn has no responsibility to print patient warnings. Physicians apparently are outside the jurisdiction of the FDA, so that they cannot be required to give such warnings to patients.

This seems to me to be at the crux of the issue. People who are being treated have a right to know what their treatment involves and what dangers they are incurring when they are treated, especially when they are given drugs for nonapproved uses.

Senator KENNEDY. It appears from what you have mentioned this morning that it is the mentally retarded and the poor people who are bearing this particular burden.

Ms. GREENBERGER. Well, I cannot generalize. I do not know. I have some knowledge based on interviews with the six women in the investigations I have done, and with regard to the Mental Retardation Institute which seems to indicate certainly they were not getting those warnings.

I do not know whether others in the population get adequate warning when they are given drugs for nonapproved use.

Senator NELSON. On the question of warnings, is it a common practice for a doctor to advise a patient to whom he is prescribing a drug, about the possible side effects?

Dr. KASE. I would hope that it would be more common than it is. Good medical practice includes just that.

Senator NELSON. That was not my question. What is the practice?

I have never heard of anybody except in a rare instance or two who said he or she got an explanation of possible side effects. Is it a common practice in your judgment? Do most doctors discuss it or not?

Dr. KASE. Most do not. But that only adds to the need for patient information, some mechanism of judging from the package insert for the patient.

Senator NELSON. But your response to the doctor who says that this would add to the anxiety in the patient would be what?

Dr. KASE. I think the answer would be it would add to the specificity and usefullness of his therapy.

Senator NELSON. You would not leave it up to the discretion of the doctor as to whether or not he would receive a simplified package insert?

Dr. KASE. No. I was careful to note that it would be directly with the purchase of the drug.

Senator NELSON. So then what you are saying is that you would require that every prescription issued for any purpose for any patient have a discussion of its indicated use and possible side-effects?

Dr. KASE. Yes; duration of therapy, usefulness, et cetera.

Senator NELSON. You would not make any exception to that?

Dr. KASE. No. I would rather have that certainly than try to create some sort of controlling legislation over the profession or the industry. I think those have proved not to be useful.

Senator KENNEDY. Senator Schweiker.

Senator SCHWEIKER. Thank you, Mr. Chairman.

I just want to ask Dr. Kase one question, elaborating on one of his recommendations.

Doctor, you suggest in your summary of suggestions: "review FDA procedures controlling clinical trials, particularly in mechanisms for the limitation of distribution and availability of experimental drugs approved for one use but not approved for other."

To get a little more specific, what kind of mechanism or procedure in your mind might be set up to cover a case like this.

Dr. KASE. I think one suggestion would be to have every prescription in a given area for that particular drug redeemable on call to find what it was used for and what the results were. I do not think that is a particularly difficult data acquisition problem.

Senator SCHWEIKER. Redeemable on call?

Dr. KASE. By an agency of some regulatory area in government.

Senator SCHWEIKER. You mean on the basis that it might have been used for an unapproved purpose, or on any basis?

Dr. KASE. Depo-Provera might possibly have been used in 1,500 women in Tennessee to combat endometriosis, but it could also have been used for contraceptive purposes.

You need to be able to seek out what use the drug was found for and some random redeemable statement should be required—where did that prescription go, and what was its use?

Senator SCHWEIKER. You think it should be made a matter of law or regulation to prohibit the use of medicines or drugs for nonapproved uses?

Dr. KASE. I could hardly suggest that in that I have used Depo-Provera in isolated instances myself in the practice of medicine, and I would do so again.

Senator SCHWEIKER. That is all I have.

Senator KENNEDY. I want to thank all of you for coming. We want to thank you particularly, Anna; you have had difficulties; you have been abused. It is because of instances of outrageous treatment like this that we are holding these hearings; and we are going to do the best we can to try to assure that it does not happen to other people as it has happened to you.

The fact that you have come here this morning and told us your story is an indication of your great courage, and I want to thank you very much.

Our next witness is Dr. Leonard Brooks, New Woman's Clinic, Washington, D.C.

Dr. Brooks is presently Director of the New Woman's Clinic in Washington, D.C. He is an obstetrician-gynecologist, and from 1970 to 1972 he worked with the Southwest Tennessee Family Planning Project.

Thank you for being with us this morning, Dr. Brooks.

We are going to hear from Dr. Brooks and then move along with Dr. Hutcheson and Dr. Brown. We understand that there is only one daily plane going back to Tennessee, so we are continuing through the lunch hour.

Dr. Brooks.

STATEMENT OF LEONARD BROOKS, M.D., NEW WOMAN'S CLINIC, WASHINGTON, D.C.

Dr. Brooks. Senator Kennedy and friends, you just used the word a moment ago, "outrageous." I feel alone. I do not have a phalanx of bureaucrats supporting me here, and I am alone, and I have two options now that you have invited a malpractice litigation in a public forum and used the word outrageous in defining our work in Tennessee.

My two options are to shut up and go home, and let this be one-sided, or to speak my peace.

Senator Kennedy. That is why we invited you.

Dr. Brooks. All right, and I will speak my piece.

Second, I notice that this is a group almost exclusively of middle aged males, dictating to women how they are going to control their reproductive lives, and I personally consider this to be a continuate oppression of family planners in this country—so my piece.

Before I get started, I have one brief comment about this new drug application that everyone is mentioning so casually and so repetitively here. It would seem all we have to do to get birth control methods studied in the United States is submit an application to the Federal Food and Drug Administration but the FDA is externally biased against birth control agents.

They have their mechanisms of obstruction, and I have lived through these mechanisms, and I would feel free to document them subsequently, but, anyway, back to Tennessee.

Tens of thousands of Tennessean women are suffering because they are not in control of their fertility. The disease is a chaotic life—a life disordered by accidental and unwanted pregnancy. Daily our women are sentenced by inadvertent pregnancy to compulsory motherhood, to loss of self-asteem, to denial of self-actualization and to instant poverty. Where other methods have failed many have had a pregnancy free interval by use of Depo-Provera. A sensitive government eases the additive and cumulative pain of so many of its people.

Pepo-Provera provides a measure of healing solace. Following is a list of people who have, who are, and who hopefully will continue to benefit not only in Tennessee but across this land as well as throughout the world:

1. Nursing mothers. Oral contraceptives do suppress milk production in some women, whereas Depo-Provera does not interfere with milk production. So for some women Depo-Provera injections provides sustenance for the child and freedom from unwanted pregnancies simultaneously.

2. Mental retardates. Often—usually—there is no alternative to injectable contraception in the presence of a brain-damaged adult. In such circumstances accidental pregnancy further degrades a family unit.

3. To cover a surgical interval. Some women return to a hospital after having had a baby for a tubal ligation. These troubled people are protected for three to six months by a shot given in the delivery room.

Their options are broad, and they can have their child receive some kind of maturation, and then return for their elective tubal ligation.

4. Women who lack privacy in their contraceptive lives. Many young people do not enjoy the dignity or privacy in a crowded home,

or their personal possessions are not immune to the assaults of suspicious parents. Their pills are stolen.

5. Domiciliary use. Many years ago in the United Kingdom, the family planning workers in Newcastle-upon-Tyne pleaded for the means of injectable contraception so that people living in grinding poverty and without transportation might be supplied at home. In a rural setting—such as Southwest Tennessee—many patients can be reached only by a visiting nurse. Yet we might go to them instead of insisiting that they always come to us.

6. Contraceptive failures. Many women become bloodied by intrauterine devices, and some become hypertensive on pills. Injections do circumvent both problems.

So in a capsule summary, these groups of people are the ones who were offered Depo-Provera on a voluntary basis. We offered it to nursing mothers, mental retardants, their guardians, protectors, their families.

We offered it to women undergoing a surgical interval, women who lacked privacy in their contraceptive lives. Those women who could only be contacted at home, we hired a domiciliary nurse who would make house visits to see that every woman in the county was contacted if she wanted to be protected against pregnancy.

In medicine, one is always searching for protein conduits of learning, of opportunity and of motivation. For some of our people, for many of our people, and for other peoples throughout the world, injectable contraception can bring order out of chaos and infuse into vulnerable lives the promise of control.

It is the means of self defense. So that when they come to us in Tennessee and knock at our door, our door is more fully open, so that when they ask of us for our help, it can be better given.

Of course a truly sensitive government will see to it that the suffering of its people be healed.

Senator KENNEDY. Doctor, we want to thank you for your testimony.

It appeared to me from the statements that were made by Dr. Edwards that he was certainly sensitive to the motivation for the use of this drug; but you cannot avoid the fact that the principal instrument of government, the Food and Drug Administration, which is charged with indicating whether drugs are safe or experimental, has indicated that this is still an experimental drug for these purposes.

Dr. BROOKS. There is a furious bias against birth control on the part of the Food and Drug Administration. We have used Depo-Provera for nursing mothers ever since 1963, and in the treatment of far advanced cancers.

As a death control agent it gets instant approval but as a birth control agent, it is still hung up in limbo, and Depo-Provera is not the only agent that is held up because it is largely a birth control agent.

It is a bias. It is a furious bias, a blind bias on the part of the FDA.

Now is the time to mention the three methods of obstruction. I know this. I have been through this. I have tried to get Depo-Provera approved for investigational use, but the Upjohn people had studied it to death; they could not afford any more of the required studies. They had studied it in 45 nations in the world.

But the three specific mechanisms of birth control obstruction are these:

One, by regulation a new drug application has to take place within 30 days, and when they rejected my application, they did not do it in 14 days, 16 days, 25 days, or even 29 days; it was always guaranteed to be the 30th and last allowable day.

Two, the regulation also states that the rejections have to be done by telegram. Did I ever get a telegram? Never; always by conversation only.

Three, they only ask one question at a time, and I answered the question, and would resubmit it, and then in 30 days my mail would bring me another question.

How long in life can you put up with this kind of obstruction? They can ask questions about birth control for generations. My daughter could think up intelligent questions.

So there is a bias against birth control in the Food and Drug Administration. There is nothing we can do to break it, and the American people in the meantime are suffering.

Senator KENNEDY. Do you believe that is the basis for the reluctance of the Food and Drug Administration to move more quickly.

Dr. BROOKS. But why approve Depo-Provera for cancer and not for birth control?

Senator KENNEDY. Is there not a distinction in your mind between a terminal case of cancer and the whole problems of contraception in a young, healthy woman?

Dr. BROOKS. There is a big distinction. You as a male are faced with birth, but as a middle-aged male you have not been victimized in your productive life. It is not an issue to you any more, and you are not a woman. [Laughter.]

Did you see the four or five men sitting here? No woman represented, and no birth control representative here.

You know ever since Margaret Sanger was sentenced to prison in Brooklyn in 1917 there has been this harassment, and it continues.

Senator KENNEDY. What about Marcia and Anna? I thought they were qualified representatives.

Dr. BROOKS. One swallow does not make a summer either. [Laughter.]

Senator KENNEDY. Seriously, should a physician be able to place himself above the Food and Drug Administration with regard to the use of drugs for nonapproved purposes?

Dr. BROOKS. Depo-Provera is something all my colleagues are closely familiar with, and if you are sensitive to the suffering of the people, how else can we help our people? Harry Truman said, "the buck passing stops here," and with the doctor it stops with me, and if I have the capability to uplift a person's life in some small measure, I will do it with the agents at hand. There is no alternative.

Senator KENNEDY. So you believe that individual physicians should be able to prescribe a drug that has not been approved for those purposes by the Food and Drug Administration?

Dr. BROOKS. We made every effort to get it approved, Upjohn and I submitted and resubmitted applications, and it is an ongoing hassle with them. We tried to become legitimate and get into a study program. We could not.

Senator KENNEDY. Therefore you approved it on your own in effect.

Dr. Brooks. We had to. There was no alternative. There was a bias against birth control in favor of death control.

Senator Kennedy. Senator Nelson.

Senator Nelson. I was not here at the beginning of the testimony this morning. What is the legal status of this drug now respecting use for birth control purposes? Is it under an IND now?

Dr. Brooks. It has been since 1962.

Senator Nelson. It has not been changed?

Dr. Brooks. Not at all. More questions—incessant questions—and in the meantime so many questions, such questions as will the person ever be able to have a baby again? This is something that can never be answered 100 per cent. There have been all kinds of studies, workers from Brazil. from all of the countries around the world. No one really believes this. This is a phantom.

Senator Nelson. In 1962 amendments to the Food and Drug and Cosmetics Act offered by Senator Kefauver were enacted by the Congress. The 1938 act required proof of safety. The 1962 amendment required that there must be produced substantial evidence of efficacy as well as safety based upon adequate and well-controlled studies. The definition of substantial evidence was spelled out carefully in the law.

Are you saying that the requirements of that law have in fact been met by the studies that have been produced?

Dr. Brooks. Yes, or I would not be using it.

Senator Nelson. How do you reach that conclusion in view of the fact that it has been demonstrated to be carcinogenic under certain circumstances?

Dr. Brooks. Well, it is carcinogenic in beagle hounds only, not in rats, mice or other primates or humans, in only in that part of the breast of a beagle hound which has no corollary in humans.

The only possible area of the human that I know of that is susceptible is the salivary gland, and I do not think that is very relevant.

Senator Nelson. You are aware that there has never been adequately documented proof that any chemical compound that causes carcinoma in an animal will not cause it in human beings?

Dr. Brooks. Run that by me again. [Laughter.]

Senator Nelson. In any case, where a compound causes carcinoma in animals, there has never been developed adequate scientific evidence that it will not do the same in the human species, in no case at least with any of the scientists that I have talked with in the field.

You say it might be one case in millions?

Dr. Brooks. You are mistaken there. It is zero cases in a million. It has never hapened.

Senator Nelson. This is what they are saying about DES, about 25——

Dr. Brooks. Let's talk about Depo-Provera.

Senator Nelson. You said it never happened. DES caused carcinoma——

Dr. Brooks. You asked me to talk about Depo-Provera. That is what I am talking about. No malignancy has ever occurred with the use of Depo-Provera in a human being.

Senator Nelson. All I said is that it has occurred in an animal. There has never been a case that I can find out from any scientist—and I have asked the question many times—in which a chemical caused carcinoma in an animal that you could prove it would not cause carcinoma in a human.

That is all I said, so if you have carcinoma in an animal, and there are alternative methods of birth control, then is it not a dangerous matter to put it into general use?

Dr. BROOKS. You were dozing just now because I pointed out many times there are no alternatives.

Senator NELSON. There are, I think, alternatives.

Dr. BROOKS. On a voluntary basis, if a woman says, "You are not going to stuff an intrauterine device in me, and I think from the hearings on the pill that the pill is unsafe"—yet she wants protection against pregnancy, she may accept Depo-Provera where she would reject everything else—and frequently does.

Senator NELSON. All I am saying is since it does cause carcinoma in one instance, are you suggesting that despite that you would prescribe this drug for general use?

Dr. BROOKS. Yes.

Senator KENNEDY. Thank you very much.

Senator NELSON. I would just like to insert in the record a quotation with respect to Dr. Edwards testimony regarding the incident in 1972.

[The quotation referred to was not available for the record at time of printing.]

Senator KENNEDY. Our next witness is Dr. Robert Hutcheson, Jr. Dr. Hutcheson received his masters degree in public health from Johns Hopkins University in 1965. Since then he has held various positions with the Tennessee Department of Public Health. Presently, his duties as Assistant Commissioner include directing the statewide family planning program. Accompanying Dr. Hutcheson is Dr. Stephen Moore. Dr. Moore has been working in family planning evaluation at the Tennessee State Health Department for two years.

Gentlemen, welcome to the Health Subcommittee.

STATEMENT OF ROBERT HUTCHESON, JR., M.D., TENNESSEE DEPARTMENT OF HEALTH, DEPARTMENT OF FAMILY PLANNING, MEMPHIS, TENN.

Dr. HUTCHESON. Dr. Moore could not be with us today.

I would like to tell you briefly about our experience with the progestational agent, Depo-Provera (DMPA) in the Maternal Health, Family Planning program in Tennessee. Our efforts to deliver family planning services through the 91 rural County Health Departments throughout the state began to expand in March of 1970. Within a short period of time we were receiving requests from several rural health departments to provide them with a contraceptive agent for their patients who could not take the pill and who had contraindications to the intrauterine device.

At that point we knew the injectable progestogens had not been licensed for general contraceptive usage even though they had been approved and were being used for threatened abortion, adenocarcinoma of the endometrium, endometrioses, and the oral provera was being used as a provocative hormonal pregnancy test. We were in a dilemma about whether or not to make Depo-Provera available for contraceptive usage for those unable to use other methods. Some of the special circumstances which we received requests for DMPA were for:

1. Mothers who were breast feeding their infants and for whom estrogen containing birth control pills would have been contraindicated because of its negative effect on quantity and quality of breast milk.
2. Women who had finished their childbearing and who wanted to use "the shot" until they could arrange to get their tubes tied.
3. Women who had demonstrated by several accidental pregnancies their inability to properly use the pill and who had already expelled an intrauterine device (IUD).
4. Women who had not tolerated an IUD but also had medical contraindications to the oral contraceptives; that is, high blood pressure, history of blood clots, recent hepatitis, or cancer of the cervix.

Thus, our dilemma then became one of whether to provide a means of preventing unwanted pregnancy for these women with special circumstances or let them take their chances on another pregnancy, because we did not have any FDA approved contraceptive to offer them. The alternative of not meeting the need in these special circumstances and thus remaining secure in the knowledge that we were strictly following the recommendations issued by the FDA did not seem the best alternative. If not provided with a reliable contraceptive method these women would probably go on to conceive an unwanted child and then either bear the child or resort to a life-threatening illegal coathanger abortion. We felt that termination of unwanted pregnancy was not a preferred alternative to prevention of pregnancy, even if safe medically supervised abortion were available in Tennessee, which it was not.

In reviewing the medical literature on Depo-Provera we came to realize that many of the initial reasons for reluctance to use the drug were slowly being removed by medical studies. A major cause for concern was unstudied return to fertility after using the injection.

In 1970 Gardner and Mishell analyzed the bleeding patterns and return to fertility in 43 women after they had received Depo-Provera for an average of 15 months each. They found 93 percent of the patients had evidence of regular ovulation by 18 months after the last injection. When addressing the same problem of return to fertility, McDaniel in Thailand published a pregnancy rate of 87 percent in 37 women who discontinued Depco-Provera with the expressed desire of becoming pregnant. He compares it favorably to Tietze's rate with the IUD of 88.3 percent at 12 months, and Satterthwaithe's experience with the contraceptive pills where he found 94 percent conception rate in 12 months.

McDaniel concluded that Depo-Provera should be made available to women even if they want to have more children later on in their childbearing career. McDaniel who is running a large family planning program in Northern Thailand has progressed since his first publications on Depo-Provera to build up the largest single experience with the drug.

He now has 20,000 users with a total experience of 400,000 women months. Sixty-five percent of his 9,000 new acceptors each year ask for Depo-Provera over the pill, IUD, or tubal ligation. Because of our interest in continuing to use Depo-Provera we have stayed in close contact with Dr. McDaniel regarding his continuing experience with the drug.

We have received from him an analysis of his latest data not yet published on 135 women who stopped using Depo-Provera to become pregnant.

I might add that 82 percent had conceived within 14 months of stopping the contraceptive. Considering the variance in desire for the pregnancy among these women we are convinced that the work of McDaniel, Gardner and Mishell has essentially laid to rest the potential problem of unpredictable return to fertility after the usage of Depo-Provera. We were impressed by several other facts in the Depo-Provera literature which have influenced our policy at the State Health Department. First the need being expressed by the women coming into rural family planning clinics was for a birth control method which would not fail. Many of them did not ever want to get pregnant again and if they could have afforded to do so, would have had a tubal ligation.

The failure rate of Depo-Provera in the literature is lower than any other contraceptive method available except for tubal ligation. The studies quote an accidental pregnancy rate between 0 and 0.5 pregnancies per 100 woman years. Thus, when women wanted tubal ligations we could put them on Depo-Provera and nearly guarantee they would not become pregnant while waiting to become sterilized.

The need for a method of contraception without the commonly recognized side effects of estrogen was another factor in our decision to make Depo-Provera available for the family planning clinics in Tennessee. Literature has proven to our satisfaction that alteration of serium proteins, alteration of fibrinolytic activity of veins, or effects on blood pressure are side effects of estrogen in the pills containing contraceptives but not of Depo-Provera.

Thus, in women who have high blood pressure or blood clotting problems, and therefore cannot use oral contraceptives, there is a need for a strictly progestational agent which will reliably protect against pregnancy. Also, the situation with breast feeding mothers has been addressed in the literature. While estrogen has been proven to have a negative effect on the amount and quality of breast milk in lactating mothers Depo-Provera has been shown to have no effect on either the quality or quantity of breast milk produced. Thus, the unmet need of mothers in the rural areas of Tennessee to prevent back to back pregnancies without compromising the nutrition of their breast-fed infants is met with Depo-Provera.

The simplicity of the method, the absence of any estrogenic side effects, the high level of reliability, combined with good acceptability despite the unpredictable bleeding pattern encountered with its use, suggested that Depo-Provera should have a place in our "contraceptive cafeteria" approach to family planning in Tennessee.

When I say "contraceptive cafeteria" approach I mean that the patient has a right to make a decision on the type of drug that would be available to her, and that this is one method that in my opinion needs to be made available.

Senator KENNEDY. Even if it has not been approved for this purpose by Food and Drug Administration?

Dr. HUTCHESON. Yes.

Senator KENNEDY. What is the reason for that?

Dr. HUTCHESON. I have just one more page, and then I would be delighted to come back and answer that. Some of this may be answered in the next page or so.

Senator KENNEDY. Very well.

Dr. HUTCHESON. In responding to the need expressed by our county health department family planning programs we decided to make Depo-Provera available for a limited contraceptive usage.

Because of our uncertainty one and a half years ago about the return to fertility with Depo-Provera, we recommended it only for those women who were finished having their family and wanted a child-limiting contraceptive. We made it clear that the drug was not the contraceptive of first choice, and that its use was to be restricted to the special circumstance outlined above. We drew up a consent form which has been recommended by the State Health Department for signature by any women contemplating use of Depo-Provera. This was done in order to make sure patients knew of all the side effects before starting the method and also knew of its unpredictable return to fertility, which has since been proven to be similar to the IUD and Pill. A copy of the consent form is appended.

As of February 1, 1973, we have 57,000 active patients on the family planning program in Tennessee. Distributing the 57,000 by method of contraceptives, there are 44,000 using the oral contraceptives, about 6,000 using the IUD, about 6,000 using condoms, foam, or diaphragms, and 942 using Depo-Provera.

Of the 942 active patients on Depo-Provera, 505 of them are in the five-county area previously directed by Dr. Leonard Brooks who has already spoken here today. The remaining 437 active patients on Depo-Provera are spread out over 90 counties with some areas of concentration in counties where the family planning program uses DMPA as an interim method until tubal ligation can be obtained, or where the program provides services for a mental institution or school for the retarded.

It has been our experience that in the selected women for whom it is chosen as the only appropriate contraceptive method, the patient is only too happy to put up with the side effects listed on our consent forms in order to be provided with a reliable means of protection against pregnancy.

Perhaps because of the narrow range of use, our patients seem more concerned about its small but potential accidental pregnancy rate than its previously feared problem of return to fertility.

If you will give me the question again, Senator.

Senator KENNEDY. Earlier you suggested that "Depo-Provera should have a place in our 'contraceptive cafeteria' approach to family planning in Tennessee."

Dr. HUTCHESON. Yes.

Senator KENNEDY. The Food and Drug Administration has not approved it for purposes of birth control.

Dr. HUTCHESON. That is right.

Senator KENNEDY. The thrust of your statement is that you have made a study and in effect you have approved the drug for people in Tennessee. I want to know what information you have available to you within your department of health that the Food and Drug Administration does not have, and whether you feel you can encourage the prescription of a drug which clearly has not been sanctioned by the Food and Drug Administration.

Dr. HUTCHESON. I am able to do that for limited circumstances now, and you are saying do we know things that the Food and Drug Administration does not know. I think we do have a few facts they have not yet received.

I think we both have access to some of the studies. I think we might have possibly what they do not have, the most recent work of Dr. McDaniel, but I believe they have the same information essentially, and they came to a different decision.

Senator KENNEDY. That is the problem, is it not? They have come to a different decision, and they do not feel that this drug should be approved for birth control purposes.

Dr. HUTCHESON. That is right. That is why we limited its use to special situations, because they do not approve of it for birth control.

Senator KENNEDY. What are the special situations? We heard from one this morning who represents the poor. Are those the special circumstances?

Dr. HUTCHESON. No. The special circumstances are outlined in my testimony, Senator.

My agency is essentially in the middle in that we are not supplying the services to many of these women ourselves but instead are supporting those who are attempting to provide services. For instance, when the physicians and the nurses in the clinic want Depo-Provera, we have provided it, and provided them the warnings for the use of it.

Now you found an instance that fell outside the special situation, and she testified today.

Senator KENNEDY. There were, as I understand it, six cases. They were the only six investigated by the research group we have heard testify today.

Dr. HUTCHESON. I am not completely sure that all six fell outside the special situation.

Senator KENNEDY. You cannot get around the fact, though, that the Department of Health in Tennessee has approved this drug for birth control purposes, and the Food and Drug Administration has not.

Dr. HUTCHESON. That is right.

Senator NELSON. May I ask a question at this stage?

Senator KENNEDY. Certainly.

Senator NELSON. Are you sure that is correct? Are the family planning clinics using Depo-Provera in Tennessee under the provisions of an IND that has been approved?

Dr. HUTCHESON. No. We attempted, as Dr. Brooks said, to get an IND number, and were unable to get it.

The reason that Depo-Provera is available to us, I think it has been brought out by others in their testimony, is because this drug is licensed but not for birth control.

Senator KENNEDY. From whom do you get it?

Dr. HUTCHESON. We get it from Upjohn.

Senator KENNEDY. Do you just send them an application, send them a purchase order, or whatever, and they send it out to you?

Dr. HUTCHESON. Right. We found out it was on State contract.

Senator KENNEDY. Do they require any followups at all?

Dr. HUTCHESON. No, sir.

Senator KENNEDY. When you contract for Depo-Provera, does Upjohn ask what you are going to use it for?

Dr. HUTCHESON. No; they do not.

Senator KENNEDY. You just have a purchase order, and they just send it to you, like that?

Dr. HUTCHESON. Yes.

Senator KENNEDY. Have you seen the rather involved consent form that has been put out by the Food and Drug Administration in relation to the research programs and projects?

Dr. HUTCHESON. Yes.

Senator KENNEDY. Then you have a form of your own; is that correct?

Dr. HUTCHESON. That is true.

Senator KENNEDY. I have read just some excerpts from the Food and Drug Administration form and yours is the following:

"I am hereby confirming a personal need for special contraceptive care and request to be given birth control injections as prescribed by the clinical physician. This injection, it has been explained to me, can have possible side effects, et cetera."

How does the signer know about the value of the drug as opposed to the side effects?

Dr. HUTCHESON. Senator, they will not know of it if the clinic physician has not explained it to them, but we have advised them to explain it.

Senator KENNEDY. How would he explain it? How would be explain that he has come to a different conclusion from the conclusion of the Food and Drug Administration?

Dr. HUTCHESON. He might have come to a different conclusion than the F.D.A. did. I think the conclusion Dr. Brooks brought out was the question of Depo-Provera causing cancer in a certain tissue in the breast of beagle hounds, and the fact is that human beings do not have that tissue in their breasts.

Senator KENNEDY. Do you have any procedures by which doctors are told how to explain this to their patients?

Dr. HUTCHESON. We have given the doctors training about this. We meet usually four or five times a year, and the subject has been brought up repeatedly.

Senator KENNEDY. Do you have forms which make the doctors aware of all the facets of this problem?

Dr. HUTCHESON. I would not call them forms, but we have sent out information.

Senator KENNEDY. Do you have copies of this information?

Dr. HUTCHESON. No.

Senator KENNEDY. Could you submit it?

Dr. HUTCHESON. Yes.

Senator KENNEDY. The information that you forward will be placed in the record.

[The following was subsequently supplied for the record:]

WINFIELD DUNN
GOVERNOR

Eugene W. Fowinkle, M.D., M.P.H.
Commissioner

STATE OF TENNESSEE
DEPARTMENT OF PUBLIC HEALTH
NASHVILLE 37219

February 22, 1973

Senator Edward M. Kennedy, Chairman
Senate Health Subcommittee
4226 Dirksen Building
Washington, D. C. 20510

Dear Senator Kennedy:

This letter is a follow-up to my testimony on February 21, 1973. You asked three questions for which I had no answers with me at the hearing. You asked that I send the answers or material when I returned to Nashville. Here they are:

(1) You wanted the material sent by us to Health Department Family Planning Clinics regarding Depo-provera. You will find a six page document which was sent out in October 1971. In addition, the Department had an all day workshop for directors of clinics using Depo-provera on July 30, 1970 at Paris Landing State Park (Tennessee).

(2) You wanted to know what percent of Depo-provera was distributed in what manner. We have records only for Depo-provera in Tennessee purchased by the Department. Until December 1972, 95% of the Depo-provera paid for by us was ordered by us but shipped directly to the clinics by Upjohn. Since December 1972, 95% of the Depo-provera paid for by us has been ordered by us, shipped to us centrally, and then shipped by us to the clinics.

(3) You asked at which medical meeting for Public Health workers was the use of Depo-provera discussed. I told you the American Public Health Association. While that is true in a small way, I find that Depo-provera was discussed at great length by the American Association of Planned Parenthood physicians at a fairly recent meeting in Detroit. Your

Senator Edward M. Kennedy -2- February 22, 1973

staff should be able to get copies of the written material produced at their meeting about Depo-provera by writing A. A. P. P. P., 810 Seventh Avenue, New York, N. Y. 10019.

Sincerely yours,

Robert H. Hutcheson, Jr., M. D.
Assistant Commissioner

RHHJr:tc
CC: A. A. P. P. P.

Senator KENNEDY. Do you have any followup, any monitoring of the people to whom you give the drug?

Dr. HUTCHESON. The monitoring is handled by the individual clinics, and I would believe that this perhaps varies from one to another in exactly what is monitored.

We encourage and nearly always get patients returning to clinics approximately every 3 months who are on the product, and they are interviewed at length by both public health nurses and the clinic physician.

We have encouraged this and tried to give clinic personnel help in this interview process.

Senator KENNEDY. Does the State health department have any ongoing process by which to monitor the use of this drug in its family planning practice?

Dr. HUTCHESON. We are monitoring where it is being used georaphically.

Senator KENNEDY. Do you have any of those reports?

Dr. HUTCHESON. No, but I can tell you that while we were at 1,400 patients, we are now down to 942, and I think that this shows perhaps the effectiveness of the FDA change in October, because it was in October 1972 they changed their package insert, and this package insert has perhaps had a big effect on the program since patient load has gone from 1,400 to 942.

Senator KENNEDY. What was in the information?

Dr. HUTCHESON. In the information it pointed out that the drug was not approved by the FDA for birth control.

Senator KENNEDY. And that brought a reduction of approximately one-third?

Dr. HUTCHESON. Well, it was coincidental with it.

Senator KENNEDY. Do your doctors tell any of the patients that Depo-Provera has not been approved by the Food and Drug Administration for birth control purposes?

Dr. HUTCHESON. Oh, yes. I think you have demonstrated today that they do not always tell it to all the patients.

Senator KENNEDY. It is not on the consent form, is it, that this use is not approved by the Food and Drug Administration?

Dr. HUTCHESON. You are right.

Senator KENNEDY. Do you think it should be?

Dr. HUTCHESON. I do not know. Do you think it should be?

Senator KENNEDY. Yes.

Dr. HUTCHESON. Okay, you have talked me into it. [Laughter].

Senator KENNEDY. Do you know if other States are using the drug?

Dr. HUTCHESON. I believe they are in Georgia, but I do not know for sure; but I heard they were.

Senator KENNEDY. Is that the only other place?

Dr. HUTCHESON. No. There is some being used in some other States, but I have no personal knowledge of it in any other States, but in meetings people talk about it.

Senator KENNEDY. Do you have a national association of the various States? Do these people get together and talk about the problems associated with these issues?

Dr. HUTCHESON. Yes.

Senator KENNEDY. Do you know if the use of Depo-Provera has been on the agenda at all?

Dr. HUTCHESON. I believe that this may have been at the American Public Health Association, but I do not recall which year that they may have had this on. Also the American Association of Planned Parenthood Physicians at their Detroit meeting.

Senator KENNEDY. I suppose Upjohn would know that?

Dr. HUTCHESON. I do not know that they would or would not, but I think one man will be testifying from Upjohn.

Senator KENNEDY. When you send out your purchase order, to whom is the drug sent? Is it sent to the Department of Health, State of Tennessee, or is it sent to the family planning clinics?

Dr. HUTCHESON. In most cases it is sent to the department of public health; in some cases it is sent directly to the clinics because the clinics can order using the same State contract, and we do have the ability to drop shift to the clinics.

Senator KENNEDY. Can you give us any breakdown as to what percentage goes to the department and what goes out to the clinics?

Dr. HUTCHESON. All that comes to the department is then shipped out to the clinics.

Senator KENNEDY. Right, but can you tell us what percentage of the family planning clinics get direct access to the material, and what percentage get it through the department of health?

Dr. HUTCHESON. I really do not know. It would be in the files.

Senator KENNEDY. When you return, could you send that to us? You understand what I am trying to find out: what percentage of the drug is mailed directly to the family planning clinics and what percentage goes in bulk form to the Department of Health of Tennessee.

Dr. HUTCHESON. Even that comes in bulk form. It is used to fill prescriptions. I am not sure what you are driving at, but I will be glad to try to give you the information.

Senator KENNEDY. What are the demographic characteristics of the population of the State family planning clinics? Are they upper class?

Dr. HUTCHESON. Twenty percent are currently on welfare, and 80 percent are currently not on welfare.

Senator KENNEDY. What would you say was the financial median of the groups?

Dr. HUTCHESON. I would say that the financial median is probably at the level of the working poor, that is, the people who do not make a lot of money but who are working.

We do not have eligibility requirements in Tennessee, that is, we do not have economic barriers to service.

Senator NELSON. The drug has been approved by the FDA for use for birth control purposes for 10 years under an IND; is that correct?

Dr. HUTCHESON. I believe that is right.

Senator NELSON. After the discovery that the drug induced carcinoma in certain circumstances in dogs, then the FDA required informed consent indicating that it did cause mammary tumors in animals.

Did I understand that these birth control clinics are not informing the user, giving the user the same information that the FDA requires if they are operating under an IND?

Dr. HUTCHESON. Good point. We applied to the FDA to let them regulate us, and they would not do it, you see.

Senator NELSON. I am a little puzzled about this. The FDA has permitted the use of this drug for birth control purposes under an IND for ten years. Why did they turn down the application for the clinics in your State?

Dr. HUTCHESON. I do not know, but it would be useful to find out from the FDA representatives here if they are turning all of them down, or if they are just turning ours down.

They could have told us perhaps if we did not meet their requirements—and I know a Federal agency must have quite a large book of requirements that need to be met—they could perhaps educate us in the things we need to do to get the IND, but we have problems.

Senator NELSON. Do these clinics apply directly to the FDA for an IND, or was the Upjohn Co. applying or assisting in applying for an IND?

Dr. HUTCHESON. I do not know.

Senator NELSON. They did not give any reason that you know of for turning down the application?

Dr. HUTCHESON. That is right.

Senator NELSON. Since they have approved it for this purpose, for investigation purposes, for ten years——

Dr. HUTCHESON. Yes, it would seem that they would have given an IND number, and then we would have had to go by every rule and regulation they have, and they could have had us there.

Senator NELSON. It may be that they wished to limit the number of experimental cases.

Dr. HUTCHESON. That could be. You know, Senator Nelson, If I may, you brought up the issue of Chloromycetin this morning—how Cormycin can be quite dangerous if it is used on a widespread basis—also you mentioned ordinary antibiotics were often used in nonapproved ways.

I would imagine from talking to colleagues in Tennessee that there must be hundreds of thousands of persons who receive antibiotics for such indications as viral infections, and this is not approved by the FDA. The problem with Depo-Provera may be a tiny problem compared to the problem you brought up of antibiotics.

Senator NELSON. I would say it probably is, but they are two different indications. One is the case of a drug being approved and in the marketplace, and the doctor proceeding because of his lack of information to use it for the wrong purpose.

Now, the doctors who are using this drug know what purpose they are using it for. The doctor who gives an antibiotic for a viral infection from a common cold, if that is the purpose for which he gave it, just does not know any better, because it does not affect any common cold virus.

If he is giving it prophylactically in an uncomplicated hernia operation, then I think almost every panel of medical experts in this country would say that is bad medical practice.

But in this case they are using it—they know the purpose for which they are using it, and I am just curious as to why they would do it without an IND.

Dr. HUTCHESON. I think, Senator, that they feel they are in a very bad position. I think they feel that they really need more research. We need a safe, effective, completely safe, completely effective contraceptive that is very easy to use, and that is very well accepted by all the people coming in and wanting the product.

We need this, and we do not have it, and so sometimes in these special situations it is either this or nothing.

If we could have more research in this area, perhaps we could eliminate this. It would seem it would be very helpful if we had better methods.

Senator KENNEDY. But of course yours is not a research program.

Dr. HUTCHESON. No, I am not asking research money for us, but I am asking for research money for those in the business of research so that we can have an approved, safe contraceptive. We need this.

Senator KENNEDY. It is a research drug, nevertheless.

Dr. HUTCHESON. Yes, it is, and yet is has been made available through a loophole, if you like, and it is licensed for other use by the Food and Drug Administration but not for this use.

Senator KENNEDY. Not for this use.

Dr. HUTCHESON. Yes.

Senator KENNEDY. Does the department of health feel it has a responsibility to monitor the drug Depo-Provera?

Dr. HUTCHESON. Would you define "monitor" so that I know what you mean?

Senator KENNEDY. After you know which clinics are receiving the drug, there are periodic examinations of the people taking it. Are the results of those examinations followed up generally?

Dr. HUTCHESON. This is being done. What you describe is being done.

Senator KENNEDY. This is being done by the State department of health?

Dr. HUTCHESON. Part of the record is available centrally. The entire patient's record is available in one place, and we have access to all of it.

Senator KENNEDY. You do a followup on this too, after you get the drug?

Dr. HUTCHESON. Oh, yes; but much of the followup is done by the county clinic itself.

Senator KENNEDY. Not by the department?

Dr. HUTCHESON. Yes, but we have a very close relationship to these clinics providing the service.

Senator KENNEDY. Do you know anything about Anna's medical record?

Dr. HUTCHESON. I do not have it with me. I can get it.

Senator KENNEDY. Is that in the local family clinic or is that in the State department of health?

Dr. HUTCHESON. An abbreviated part of her record is at the State health department. The complete record is at the health department.

Senator KENNEDY. This morning you heard her testify to the nervousness and irritability that she experienced.

Dr. HUTCHESON. No. That part of it we would not have.

Senator KENNEDY. Thank you very much for your testimony.

Our next witness is Dr. James Brown, of the Arlington Hospital & School where he is superintendent.

STATEMENT OF JAMES S. BROWN, M.D., SUPERINTENDENT, ARLINGTON HOSPITAL AND SCHOOL, ARLINGTON, TENN.

Dr. Brown. Senator, Dr. Mogan could not be with us today.

I would like to clarify a couple things, at least in terminology, as I listened to the hearings this morning. We keep referring to Depo-Provera as an experimental drug. It has never been our understanding that it is an experimental drug, and our use of Depo-Provera has not been within the context or the framework of the way we would go about doing an experimental study if we did one.

Senator Kennedy. Just to clarify our terms. Dr. Edwards indicates Depo-Provera is an experimental drug for the purpose of birth control.

Dr. Brown. What is an experimental drug? If you have a drug such as Depo-Provera that is licensed for human use at a certain dose, and for certain indications, is it experimental?

This is the question in my mind. Is it experimental again for another indication that you are using it for in human beings?

Senator Kennedy. Dr. Brown, Dr. Edwards just said this morning it is not to be used for birth control purposes.

Dr. Brown. He said the FDA has not licensed it for birth control purposes.

Senator Kennedy. That is right.

Dr. Brown. Senator, I am not an expert on Depo-Provera. As a pediatrician and as an administrator I would like to tell you about our problem and what we did and how we went about it.

In 1969, anticipating the opening of a new residential facility for the mentally retarded of West Tennessee, the facility's staff sought to arrive at some policy concerning voluntary birth control. Since our population was to consist of some 80 percent profoundly and severely retarded residents, a large number of whom were multiply handicapped, we were, therefore, also concerned with menstrual periods as they affected the residents' hygiene and general health.

Our gynecological consultant, Dr. Alan Platkin, Clinical Instructor of Obstetrics and Gynecology, University of Tennessee College of Medicine, joined with us in seeking information from other gynecological specialists, and the exeprience of other similar facilities. The Tennessee Department of Mental Health guidelines and policies were consulted, and the advice and counsel of our Parent-Guardian Association were sought.

These are our sort of PTA, the parents of our residents.

The University of Tennessee College of Medicine, with whom we are affiliated, through its chairman of obstetrics and gynecology, Dr. Stewart Fish, participated in this process. We were advised by our medical specialists that quarterly injections of an progestational product of the Upjohn Company, Depo-Provera, while not specifically licensed for the purposes mentioned above, would safely control menstruation and serve as a contraceptive should sexual exposure occur. We solicited experience from other institutions and received very positive recommendations from the Mexia State Hospital and School in Mexia, Texas, where considerable experience was reported.

In the spring of 1970, with the approval of our commissioner, a letter was sent to the parents or guardians of all post-pubertal girls, explaining and proposing the use of this agent. Initially, before, the program was instituted, we requested all of these parents and guardians to attend a Sunday afternoon meeting at our facility to receive more information, and discuss the proposal. We had about an hour's discussion, and I think, if I am not mistaken, there were 91 parents.

Senator KENNEDY. Do you have a copy of that letter?

Dr. BROWN. Yes, I think we have one.

Senator KENNEDY. Would you make that available?

Dr. BROWN. I certainly will.

[The letter referred to follows:]

BUFORD ELLINGTON
GOVERNOR

FRANK H. LUTON, M.D.
COMMISSIONER

JAMES S. BROWN, M.D.
SUPERINTENDENT

STATE OF TENNESSEE
DEPARTMENT OF MENTAL HEALTH

ARLINGTON HOSPITAL AND SCHOOL
P. O. BOX 399
ARLINGTON, TENNESSEE 38002

Dear

Arlington Hospital and School now has 380 residents and is admitting new ones monthly. We are finding the task of giving maximum care and training to this number a great one and now are attempting to devise means of reducing the time required in certain areas of nursing care in order to devote more time to other areas that would be of greater ultimate benefit to our residents.

One area to which we have given considerable thought, and about which we have sought consultation from specialists in this field, is that of reducing time in taking care of the personal hygiene of females here who are having menstrual periods. A drug, depo-provera, has been used in other institutions such as ours to prevent ovulation and menstrual periods. This drug has been approved by the Federal Drug Administration and is being marketed as a safe drug. This drug will be injected at 3 month intervals. Another effect of the drug will be to prevent pregnancy in the event of exposure. While every effort is being made at Arlington Hospital and School to prevent exposure, many of these girls will be away from Arlington Hospital and School on weekends and we cannot be responsible for their actions during their absence.

Before initiating the described program, I want to meet with the parents of the girls involved to explain, in more detail, our program, to answer any questions concerning this and to get permission from parents before entering your daughter into this program.

I have set the date for meeting with you parents for such a discussion on Sunday, April 5, 1970, at 2:00 P.M. in the auditorium at Arlington Hospital and School. I urge all parents to be present in order that we may obtain maximum understanding and cooperation. This program is being set up for the purpose of offering the best nursing care, comfort, training and protection for your girls.

I shall look forward to having you attend the meeting on Sunday, April 5, 1970, at 2:00 P.M. and feel that it is very important that you attend.

Sincerely,

Edward N. Mogan, MD

Edward N. Mogan, M. D.
Director, Clinical Services

ENM/b

Dr. **Brown**. Our higher level girls were counseled with to explain the menstrual and contraceptive effects. We have, however, very few higher level girls. Subsequent admissions were informed, and consent was requested.

Acceptance has been almost unanimous, and quarterly intramuscular injections of 150 mgms were begun. We established special monthly gynecology clinics under the supervision of Dr. Platkin to ensure yearly pelvic and breast examinations and Papanicolaou smears. At the present time, 181 female residents at Arlington Hospital and School (total population: 638) are receiving Depo-Provera injections of 150 mgms, intramuscularly, at three months' intervals.

Medical supervision and observation of this population is necessarily close, and no significant side-effects have been observed. Appended are individual statements of supervising physicians. No pregnancy has occurred in any resident after admission to the facility.

It was our impression that the risks accepted with the use of this agent paralleled the risks with other progestational hormones, and that a major objection to its more wide use was the possibility of prolonged infertility after discontinuance, up to 18 months or more following serial use.

We noted later after we received the information that beagle hounds had developed tumors in some 18 instances with the agent, our public health nurses were advised to explain prolonged infertility to each individual parent, and the possibility that in certain beagle hounds certain tumors of the breast had occurred, but not in humans.

We note that the FDA has changed the stated indications for 1973—I was just aware of it myself last week—and added a warning that the product is still under investigation for contraceptive use because of unresolved questions concerning its safety for this indication.

Our consultants have continued to advise us to maintain this program. They are being requested to again review the clinical data concerning Depo-Provera and to submit a current recommendation to us concerning its safety and efficacy.

I have included our permits and two reports.

One of the things, Senator, I suppose you are probably very aware of, that staffs of mental retardation facilities and other people who are trying to serve the retarded have the problem of human rights, informed consent in many cases, we have really no advocates.

At the Arlington Hospital and School we have no (court) committed residents, and even though we do have some individual residents at Arlington, where we really do not have a next-of-kin, we try to provide some custody, and even though the welfare have custody, so as to have adequate custody for each child.

We have currently (after checking our records) 119 out of 181 signed permits, as you have read. I am looking into the matter of how many of the remainder have not been obtained in writing, and how many of the remainder have no next-of-kin.

We have many individuals in the facility, mainly older residents, who were transferred—who were originally West Tennesseans and were transferred when we opened our new facility—from middle Tennessee.

The problem of informed consent is a problem that we have, and we need a lot of help particularly in this area, as you are well aware.

We need in many cases very good legal advice, which we have none, not only in our facility but none in the State.

There are many factors involving the rights of the retarded which are very unclear. We need guidance and help here, too.

Senator KENNEDY. Did you ask your attorney general for any help and assistance?

Dr. BROWN. Yes. Many, many times we have, and there just is not any body of law apparently in this area anywhere in the country, and it is something we are all on a nationwide basis trying to cope with.

I would be very happy if the FDA and the experts across the country who advocate Depo-Provera as a safe and efficacious drug for human use resolve their differences and come to some conclusion, so that many of us who are in the middle and need guidance and help can have it.

Senator KENNEDY. As I understand your situation, you are caught in a dilemma: the Food and Drug Administration has not approved Depo-Provera for one purpose for which it is being used, and yet your consultants to the schools have indicated to you that this use is an acceptable means to achieve the ends which you have outlined in your statement; is that correct?

Dr. BROWN. Yes, sir.

Senator KENNEDY. So you are caught in between, as you mentioned here. You hope that the people using this for unauthorized purposes and those at the FDA will be able to resolve their differences?

Dr. BROWN. Quickly.

Senator KENNEDY. What are you going to do in the meantime?

Dr. BROWN. I am going to continue the program until my consultants, in consultation with the FDA and the drug company, advise us that we can meet and go over the situation with not only our staff members but outside people, particularly our parents.

We will completely revise our information to all parents, and this program will commence immediately.

Senator, I do not think that anyone has given you any information on the unsafety of the drug for human use. We do not have it either. If we could get it, we would stop the drug today.

Senator KENNEDY. The Food and Drug Administration, which is the present regulatory agency, which has the resources—financial and research resources—to make these judgments, has indicated that it has not approved this for this purpose.

Your consultants have reached other conclusions. What we must determine is whether we are going to have individual doctors using these various drugs, or State agencies in effect substituting their judgment for the judgment of the Food and Drug Administration.

Should that be permitted?

Dr. BROWN. I would suggest perhaps that if there is this much doubt in their minds, they should remove the drug for all purposes.

Senator KENNEDY. Why is that necessary? They have approved it for terminal cases of cancer, which are entirely different.

Dr. BROWN. Yes. The original indication that I remember was for endometriosis and for threatened abortion when we started. I think they have started recommending it for threatened abortion and included another indication in the last year or two in metastatic carcinoma of the uterus. If it is safe to use in endometriosis or threatened abortion in human beings, why, I would like to know, is it not safe as a contraceptive? I am not an expert, sir, and I am just asking. I want this information.

Senator Kennedy. The FDA says there is an unresolved question of safety. That is the FDA's clinical conclusion on it.

Dr. Brown. Yes. This was the October decision I believe, was it not?

Senator Kennedy. Yes. You, or at least the clinical researchers in Tennessee, have reached different conclusions.

Dr. Brown. Well, certainly, if there is any question about its safety and the FDA had not told me what it is, my consultants would certainly find out and advise us, and we would take our people off the drug. I think we still have not quite established this, Senator Kennedy.

Senator Kennedy. You what?

Dr. Brown. I am not sure we have established what this is, at least so far as communicating is concerned.

Senator Kennedy. Do you think physicians should independently be able to decide whether or not a drug is safe?

Dr. Brown. No, I do not. I certainly do not.

Senator Kennedy. Is this not really what has happened here?

Dr. Brown. Well, I do not think the FDA has said it was unsafe.

Senator Kennedy. Unresolved questions of safety? You say there is a significant doubt, a serious doubt.

Dr. Brown. That is correct.

Senator Kennedy. That doubt on the part of the Food and Drug Administration is in no way reflected in your consent form, is it?

Dr. Brown. No, it is not.

Senator Kennedy. Is this injection given only to the retarded in the State institution?

Dr. Brown. In our facility, yes, sir, all of our residents are retarded.

Senator Kennedy. How do you decide? Do you give it to all?

Dr. Brown. No. All our post-pubertal girls with the approval of parents received.

Senator Kennedy. So if you get approval, any retarded girls can get the drug.

Dr. Brown. In our facility as residents.

Senator Kennedy. Is the drug used in other facilities?

Dr. Brown. I am not sure, Senator. I know they use it in Texas. This is where we got some information.

Senator Kennedy. In your State?

Dr. Brown. Yes, and in our State I am not certain really. I think that they may use it in the Greene Valley Institute, but I do not know the extent or nature of their program.

Senator Kennedy. Why is it used for the retarded and not for others?

Dr. Brown. As I said, the problem of providing birth control, and also the problem of menstrual periods, in a facility, among the very severely retarded, is a considerable problem. It is one we agonize over from the standpoint of the normalization principle, and try to weigh the benefits of obliterating menstruation to the resident, as compared with the benefits to the staff.

We have had many discussions of this recently in our new institution for the mentally retarded, Arlington Hospital and School, which has just gotten standards, from the joint commission on accreditation of residential facilities for the retarded, for the first time in history. We have completed a very, very voluminous self-assessment, and this was one of the problems that we tackled.

Senator KENNEDY. Is it given also to the ambulatory retarded?

Dr. BROWN. Yes. Parents and guardians seek birth control for the retarded. They seek it sometimes themselves. We have a policy of encouraging about 150 to 200 of our residents to be at home each weekend. We have a great many of our residents who have a history of sexual exploitation, and this birth control is deemed important to most parents and guardians.

Senator KENNEDY. What is the median income of the people?

Dr. BROWN. In our facility? We are in fact the only facility in west Tennessee, and we have people from indigent to rich.

Senator KENNEDY. How would you break it down?

Dr. BROWN. About like the population, Senator, I would guess. I do not know precisely.

Senator KENNEDY. As to race?

Dr. BROWN. About 50–50 in our community—48 and 52.

Senator KENNEDY. Finally, how did you obtain the drug?

Dr. BROWN. We simply ordered it from the company on a purchase order like we do all other drugs.

Senator KENNEDY. From Upjohn?

Dr. BROWN. Yes, sir.

Senator Kennedy. Do they know where they are sending it?

Dr. BROWN. Surely. Our facility is named the Arlington Hospital and School, Arlington, Tenn.

Senator KENNEDY. Do they have any idea why you want it, do you know?

Dr. BROWN. I do not know.

Senator KENNEDY. Have they ever bothered to ask?

Dr. BROWN. No; not to my knowledge.

Senator KENNEDY. Thank you very much. We appreciate very much your coming up.

Our last witness this morning is Dr. William N. Hubbard, Jr. Dr. Hubbard is the executive vice president of the Upjohn Co. of Kalamazoo, Mich. Among many other activities in the area, Dr. Hubbard has been a member of the study section, Heart Program Project Committee on the National Institutes of Health, a regent of the National Library of Medicine and chairman of the board of regents from 1965–1967, and a consultant to the Public Health Service Division of Hospitals and Medical Facilities. He was on the board of directors at Upjohn in 1968, was vice president and general manager of the Pharmaceutical Division in 1970, and became executive vice president of Upjohn in 1972.

Dr. Hubbard, thank you for taking the time to be with us this morning.

STATEMENT OF W. N. HUBBARD, JR., M.D., EXECUTIVE VICE PRESIDENT, UPJOHN CO., KALAMAZOO, MICH.

Dr. HUBBARD. I would like to thank you for the opportunity to testify before the Senate Health Subcommittee. It is my understanding from this morning's testimony that you are interested in Depo-Provera. My formal testimony consists of a brief résumé of this medicinal and then some commentary on the problems that are exemplified by the use of this agent as an injectable contraceptive in women.

Medroxy Progesterone, or Provera, is a chemical produced synthetically that is related to the natural hormone, progesterone, and is available both for injection—called Depo-Provera—and for administration by mouth. In the usual dose range, Depo-Provera inhibits secretion by the pituitary gland of hormones required for maturation of the ovarian follicle and for release of the mature ovum. Depo-Provera also changes the epithelium of the uterus from a proliferating or growing stage to a secretory or resting stage.

As has been mentioned, in the United States it is approved for use as an adjunctive and palliative treatment of carcinoma of the lining of the uterus and for a gynecologic condition known as endometriosis. In 1960, when Depo-Provera was first marketed, it was generally thought that progesterone-like substances would reduce the rate of threatened abortions. Within the last few years the lack of controlled clinical studies to prove this effect has resulted in this no longer being an approved use.

Very early in the use of Depo-Provera for its approved indications, it was observed to cause an associated inhibition of the menstrual cycle and of ovulation. These effects suggested the potential utility of Depo-Provera as an injectable contraceptive. In July of 1963, an Investigative New Drug Application was activated for human clinical studies, as well as additional animal studies, designed to determine the safety and effectiveness of an optimum dosage schedule, as well as the type and prevalence of untoward reactions.

These studies revealed that the optimum dosage schedule was 150 mg. every three months and this schedule has been studied by 54 of the 85 investigators around the world and in 3,857 women for a total experience in the United States of 72,215 woman months.

In 1966 long-term studies of chronic toxicity were begun utilizing rats, rabbits, mice, monkeys and beagle dogs; employing multiplies of the effective human dose. With the exception of the beagle dog, no significant differences have been observed between treated and control animals. In beagle dogs, however, nodules of the mammary gland were found earlier and were more persistent in the treated group than in the control group. In 1971, two of the dogs treated in this group had metastatic cancers of the breast. The significance of these findings with respect to humans has not been established.

Unfortunately, it is true that some constituent of virtually all hormonal contraceptives have been demonstrated to cause cancer in one or another species. There are no data, however, to suggest that in women using any hormonal contraceptives that there is any greater frequency of cancers than in the general population of women of the same age. Even though the risk is therefore inferential rather than demonstrated, it does demand an analysis of the risk to benefit ratio.

It is our hope that it will be possible to develop suitable conditions under which this compound may be made available in the United States for contraceptive use. The matter is under active consideration by the Food and Drug Administration and we stand ready as a company to cooperate fully with that agency in assuring that both the letter and the spirit of the Regulatory Acts are fulfilled.

Meantime the authorities responsible for registration of medicinals for sale in countries throughout the world have reviewed the scientific data submitted to them according to their requirements and with full knowledge of the regulatory actions taken by the United States Food and Drug Administration.

They have come to their own conclusions as to the risk-benefit ratio of the product, based on the contraceptive needs of their own countries and with the advice of their own medical experts. As a result, registration and sales for contraception have been recorded in 38 countries. These include such Western countries as Belgium, Denmark, West Germany, Holland, Norway, Sweden, and Switzerland. Also included are Eastern bloc countries such as Bulgaria, Poland, Hungary and Yugoslavia.

In all of these cases of sales internationally the 150 mg. vial that is generally used for contraception is produced exclusively in the plants of Upjohn subsidiaries in Belgium and Mexico. The only production of 150 mg. vials in the United States is restricted to clinical supplies for IND investigation.

A number of very interesting problems are raised by the case of Depo-Provera which have general significance:

1. The problem of species specific biology. As more and more species are used to study toxicology and pharmacology, it becomes clear that we are unable to define completely the significance of differences between species in terms of relevance to human biology. In general where it is demonstrated that an animal's metabolic pattern is significantly different from that of humans, then the likelihood of that animal's response to a medicinal agent being predictive of behavior in humans is reduced.

In the case of Depo-Provera, therefore, one is confronted with the problem that the dog is metabolically less like the human than are the monkey and the rodent insofar as resembling the human response to sex hormones is concerned; but only the beagle dog has demonstrated under treatment with Depo-Provera an increased frequency of mammary neoplasms. Such dilemmas unfortunately can only be resolved by exposing humans who have a high potential benefit to the agent in order to determine whether the inferred risk from the dog data is real.

Then comes the question of informed consent. Whether a risk is inferential or whether it is specific in some order of certainty, every medicinal agent carries with it some risk. It is always the responsibility of the physician to inform his patient of both potential benefits and risks, whether he is utilizing a new or a long-established medicinal. The custom in the United States of using written informed consent is relatively recent and it is not generally used in the rest of the world.

Whether oral or written, however, there is always a risk that some coercion may be exerted so that the consent is not freely given. This may be so subtle as the patient's basic confidence in the therapeutic intent of the responsible physician, or so overt as offering large sums of money or other rewards for participation in an experiment.

In the case of Depo-Provera, an informed consent document has been worked out cooperatively between the Food and Drug Administration and The Upjohn Company. It is clearly intended to discourage all save the most determined patients from continuing in the research programs for Depo-Provera.

Third is the responsibility of the pharmaceutical company where a medicinal is used in an unapproved fashion.

Senator KENNEDY. Just before going into that, you said, "It is clearly intended to discourage all save the most determined patients from continuing in the research programs for Depo-Provera."

Why is that so?

Dr. HUBBARD. Largely because the total numbers of patients needed to satisfy the biostatistical measures of safety and efficacy had in most instances been completely satisfied.

Unfortunately, there was some misunderstanding on the part of others when they sought an IND, and it was not granted. The reason is a technical one.

Adequate data had already been collected save for a small number of residual questions involving long-term followup of patients that would not be helped at all by adding new individuals.

Thus, there was no purpose in encouraging large numbers of new patients under investigation or protocol because the numerical requirements had largely been satisfied.

Regarding unapproved use of a medicinal, this problem arises almost exclusively where a compound has been marketed for an approved use, but where physicians may independently use the drug for indications that have not been reviewed or approved by the Food and Drug Administration. For instance, the most recent Medical Letter—an independent report on therapy from experts in the field—has referred to the utility of Depo-Provera in the treatment of carcinoma of the breast and carcinoma of the kidney.

Reports in the scientific literature have described some observations of these utilities. These published studies were not sponsored by The Upjohn Company; however, and IND is now in force to study Depo-Provera in the treatment of breast and kidney cancers under the usual constraints of the regulatory act.

In the absence of an IND, we would not supply the drug for such investigation purposes. Under the regulations, none of our promotional materials may make reference to these described utilities and our sales force may not initiate discussion with physicians regarding these uses. The physician, however, is entitled to undertake these unapproved uses.

Senator KENNEDY. Is that good or bad?

Dr. HUBBARD. It depends on the circumstances. I think it is necessary. I think the circumstance under which a physician is ethically entitled to undertake a use that has not been validated by his peers and by the FDA is a very stringent one, that is to say, I am not proposing that this should be done casually or without constraint.

Senator KENNEDY. Are you satisfied that those conditions or restraints exist today?

Dr. HUBBARD. They exist. Unhappily they are not universally practiced.

Senator KENNEDY. So what happens?

Dr. HUBBARD. I think, sir, in all fields of human endeavor there are those who do not fulfill their mission as they should. I am persuaded that in the medical profession the vast majority do fulfill that mission. The exceptions have to be dealt with as such.

I could not agree more with what Dr. Edwards said this morning, that we need much more effective peer review techniques. The accountability of the physicians to his peers, I think must be enhanced.

Senator KENNEDY. Apparently the State of Tennessee is a complete exception.

Dr. HUBBARD. That is a little broad.

Senator KENNEDY. Why do we not continue, and I will come back to that.

Dr. HUBBARD. A different circumstance exists where the company is sponsoring research under an IND preliminary to New Drug Application for the new use of a compound. In the case of Depo-Provera, over 50 publications in the scientific literature on the contraceptive uses of Depo-Provera have appeared and many presentations at scientific meetings on this subject have been made. It is safe to assume that specialists in obstetrics and gynecology are quite familiar with the contraceptive use of Depo-Provera.

A large number of physicians has had over 10 years' experience in the use of Depo-Provera for its approved indications. Since it would be inappropriate for the company to supply the drug directly to physicians who had declared their intention to use it for an unapproved use, the question reasonably arises as to the discipline the company utilizes in avoiding this error.

In the first instance we avoid all positive promotional efforts and make no reference to the contraceptive uses of Provera, either in printed material or in the "Detail" materials supplied to salesmen. Since it is customary to inform the marketing groups of the progress of major research efforts, abstracts of scientific literature are made available to them, but with the clear prohibition against these documents or their contents being used in a sales effort.

Where physicians or groups write us for information regarding the contraceptive uses of Provera, we tell them routinely that we are unable to provide any information except to approve investigators working under the IND. We will give reference citations to the published literature which is available to them under any circumstances; but will not comment upon that literature.

Senator KENNEDY. Why was the drug shipped to Arlington Hospital in Tennessee?

Dr. HUBBARD. We, so far as I can determine, had no knowledge of the intent for which this drug would be used, that is, for an unapproved purpose at that place.

Senator KENEDY. For what purpose could that quality of the drug be used in the Arlington Hospital?

Dr. HUBBARD. I do not have the number of vials, Senator, that were purchased at any one time by this group.

Senator KENNEDY. I understand from the testimony that it has been purchased every 3 months since 1969.

Dr. HUBBARD. Well, we have indicated to our marketing groups that they should be most particularly on the lookout—and this we did last August—for orders from any source that could reasonably be inferred as being intended for an unindicated use.

Senator KENNEDY. After having listened to the public testimony this morning, are you going to send the drug to Arlington if they request it?

Dr. HUBBARD. I think we will ask them, if we find an order from them, what their intent is.

Senator KENNEDY. You have heard their intent. They testified to it this morning. Based upon their public and open testimony would you—

Dr. HUBBARD. No, we would not.

Senator KENNEDY. You would not send it to them?

Dr. HUBBARD. No.

Senator KENNEDY. What about the family clinics in Tennessee?

Dr. HUBBARD. The form in which our orders come to us do not reveal the ultimate location in the State of Tennessee. They come as a blanket order from the State purchasing agent.

Senator KENNEDY. We just heard from representatives in the department of health in Tennessee who indicated some came in bulk, and some went to various family planning clinics.

Dr. HUBBARD. I believe, sir, they mentioned county health departments.

Senator KENNEDY. Now that you have heard this testimony of how it is going to be used in these centers, what are you going to do about it?

Dr. HUBBARD. We have already interrupted sales to these departments in Tennessee, and the last one that we have listed in our records is either late May or July of last year, I have forgotten the exact date. It has been a number of months now.

Senator KENNEDY. You have not sent any since late May or July of last year?

Dr. HUBBARD. We have had very limited time to do a detailed search of our records. This is all in the computer file, but in the time that was available our search did not reveal any purchases since the last of 1972.

Senator KENNEDY. Would your computer feed out where the drug Depo-Provera is being used or being sent now in this country?

Dr. HUBBARD. It is not in the existing programs of the system, but I am sure that given enough time the programers could develop some way of doing it.

Senator KENNEDY. It would not be terribly complicated?

Dr. HUBBARD. Well, I am not a programer.

Senator KENNEDY. But, as I understand, there are 12 approved testing areas; is that correct?

Dr. HUBBARD. At the present time I am sorry I do not know the exact number.

Senator KENNEDY. As I understand, there are 12 approved, and we will put those in the record.

I would think the people at Upjohn would understand what there were 12 approved programs, and I would wonder what the company policy is in sending out the drug to other areas.

Dr. HUBBARD. The company policy is quite clear, and that is that the drug should not be distributed for unapproved use.

Senator KENNEDY. Do you inquire as to what use they are going to put the drug?

Dr. HUBBARD. We now do precisely that.

Senator KENNEDY. Since when?

Dr. HUBBARD. Last summer.

Senator KENNEDY. What do you ask?

Dr. HUBBARD. What they intend to use the drug for in the case of those places like family planning clinics where there is reason to infer what they intend to do with it, and we simply ask them.

Senator KENNEDY. Do you do that for all experimental drugs?

Dr. HUBBARD. This is an unusual problem. Experimental drugs by and large do not fall into this difficulty because they are under an IND, and we control quite precisely where they go. This problem arises where there is an alternate route of access.

Senator KENNEDY. Are you familiar with the form that must be filled out on how the experimental drugs are used?

Dr. HUBBARD. I am not sure of your question.

Senator KENNEDY. How do you or your company derive the information on how this drug will be used?

Dr. HUBBARD. We go all the way back to the point of initiation of the order of purchase.

Senator KENNEDY. Then you ask them——

Dr. HUBBARD. We have asked people at that level to inspect the origin of each order for purchase, and where there is any reason to infer that this is for an unapproved use, the order should not be filled.

Senator KENNEDY. Have you turned any down?

Dr. HUBBARD. Yes.

Senator KENNEDY. Would you tell us which ones have been turned down?

Dr. HUBBARD. I would have to refer to the record to be precise, but they have been turned down.

Senator KENNEDY. Do you think the physicians should have the latitude, on the basis of their own independent judgment, to use a drug for a purpose other than for which it has been marketed and tested?

Dr. HUBBARD. Yes, not all physicians, Senator, and not under all circumstances, but asked as a blanket question, the answer must be yes.

Senator KENNEDY. Who should determine the circumstances or those conditions?

Dr. HUBBARD. I think it has to be a judgment between the man who has to seek the IND and the judgment of his peers and the patients.

Senator KENNEDY. Would you support legislation which would prohibit a physician from prescribing drugs unless the physician were subject to peer review?

Dr. HUBBARD. I would have to read the legislation very carefully in that spirit. I would not have reservations if the uses were purely investigational, but we would have to be very careful about what we meant by approved. If it is extended to include unapproved dosages, to whether you use a drug or do not use it, or how long you use it— I would be hesitant to be interpreted as being in favor of expanding the definition of investigation to that extent.

Regarding Depo-Provera, in cooperation with the Food and Drug Administration, a warning has been inserted in the labeling of Depo-

Provera that its uses for contraception is investigational and is not an approved indication.

Finally, marketing staff have been asked to be alert to orders that imply beyond reasonable doubt an intention to use the drug for an unapproved use. Because of its wide availability for approved uses, this latter effort is difficult and if pursued too energetically runs the risk of having the company intrude on the legal right of the physician to utilize medicinals as he judges to be in the best interest of his patient. The dosage form most suitable for contraception is not made available for sale in the United States.

I trust that these introductory comments have been useful to the purposes of the committee and I will be glad to respond to any further inquiries that you may have.

Senator KENNEDY. I want to thank you very much, Dr. Hubbard, for your appearance here. It has been very helpful.

At this time I order printed in the record all pertinent material submitted in conjunction with this hearing.

[The following was subsequently supplied for the record:]

INJECTION CONTRACEPTION CONSENT FORM

I ———————————— am hereby confirming a personal need for special contraceptive care and request to be given a birth control injection (shot) as prescribed by the clinic physician. This injection has been explained to me as having some known side effects, but the value of this special medication to me far outweighs the side effects. The two major known side effects are:

(*a*) an irregular menstrual pattern following the shot, which sometimes leads to periodic heavy bleeding during the first few months, or no monthly periods while on the shot.

(*b*) a possibility of a delay in the ability to have children following discontinuation of this shot. I understand that if I have trouble getting pregnant after stopping the injection, treatment is available.

————————————
(Signature)

————————————
(Address)

A CONSENT FORM OF STATE FAMILY PLANNING CLINICS

I request to be given the birth control injection (shot) knowing that it has not been approved by the Food and Drug Administration for general contraceptive usage.

————————————
(Signature)

ARLINGTON HOSPITAL AND SCHOOL
Arlington, Tennessee

PERMIT FOR DEPO PROVERA PROGRAM

I, ______________________________(father, mother or legal guardian) of ____, now a resident of Arlington Hospital and School, give my permission to enter her into the program designed at Arlington Hospital and School to use depo provera.

This drug is to be injected every three months for the purposes of preventing menstruation, thereby making resident more comfortable and to lessen nursing care.

A second purpose is that of preventing pregnancy in the event of exposure.

____
PARENT OR LEGAL GUARDIAN

____
RELATIONSHIP

DATE ______________________________

ENM

STATE OF TENNESSEE,
DEPARTMENT OF MENTAL HEALTH,
ARLINGTON HOSPITAL AND SCHOOL,
Arlington, Tenn.

REPORT ON DEPO-PROVERA PROGRAM

The Depo-Provera Program has been in effect at Arlington Hospital and School since April of 1970. At the present time there are 181 girls on this program. For the past two years, 51 of these girls have been my patients. The only side effect that I have observed has been an occasional break-through bleeding. The spotting has been no problem and has certainly been easy to care for, compared to a regular monthly menses. No pregnancy has been reported. In my opinion this is a safe drug.

ALBERT HEROS, M.D.,
Assistant Clinical Director.

STATE OF TENNESSEE,
DEPARTMENT OF MENTAL HEALTH,
ARLINGTON HOSPITAL AND SCHOOL,
Arlington, Tenn.

DEPO-PROVERA EFFECTS AND SIDE-EFFECTS

One hundred and twelve ambulatory, mentally retarded females are receiving 150 mg of Depo-Provera IM every three months. Menses have been effectively controlled in 95–98% of patients treated.

Only 10–15% have shown noticeable side-effects; of these, less than 1% have demonstrated prohibitive side-effects. The most common side-effects have been: (1) Occasional vaginal spotting (approximately 12%); (2) Mild breast engorgement (8%); and weight gain (approximately 15%). Two patients have developed transient hypertensive episodes which may or may not be attributable to this medication alone.

JOAN SHORT, M.D.

Official Upjohn Consent Form

9/19/72
1

Exhibit B

REVISED DEPO-PROVERA WRITTEN INFORMED CONSENT FORM
FOR CONTRACEPTIVE STUDIES

IMPORTANT NOTE: This is NOT the same informed consent form that you signed before. It has been changed to bring to your attention that breast cancers have developed in some beagle dogs undergoing long-term tests with injections of Depo-Provera. Please read it carefully.

This is to certify that I, ______________________________, hereby agree and consent to receive an experimental drug called Depo-Provera every three months under the care and supervision of Dr. ________________________. I understand that this injection will be given to me in an attempt to keep me from becoming pregnant. I have been told that tests in dogs injected with this drug showed that some of them developed tumors in their breasts. Some of these tumors were cancer and spread to other organs. It is not know whether or not similar tumors or cancers will grow in my breasts after receiving the drug.

It has been explained to me that there are available other non-experimental methods of preventing pregnancy such as pills, vaginal creams, jellies, foams, diaphragms, various devices which are inserted into my womb and use of a rubber (condom) by my husband. The effectiveness of these various methods of contraception, as well as the advantages and disadvantages of each method, has been explained to me. Surgical sterilization of myself or my husband (along with its risks, advantages and disadvantages) has been explained to me as a nonreversible method of contraception. I have also been told of the effectiveness of Depo-Provera.

I have read and understand the pamphlet prepared by the American Medical Association, American College of Obstetricians and Gynecologists and the Food and Drug Administration informing users of the pill about the possible problems which a woman may encounter during its use. I understand also that Depo-Provera is similar to the pill in that I may have some of the same problems occurring that are mentioned in the pamphlet such as blood clots, tender breasts, nausea, vomiting, weight gain, weight loss, spotty darkening of the skin of the face, mental depression, elevated levels of sugar and fatty substances in the blood, dizziness, loss of hair, increase in body hair and increased or decreased sex drive.

It has been explained to me that it is quite likely that I will have [illegible] vaginal bleeding, completely irregular menstrual cycles or no menstrual bleeding at all as a result of the Depo-Provera injections. I also understand that the injections may have some effect on the amount of estrogenic and adrenal hormones produced in my body and that the importance of these changes is still being investigated.

I understand, also, that after a woman stops taking Depo-Provera there may be an unpredictable and prolonged delay before she is able to become pregnant or may be unable to become pregnant at all. Because of the possibility of an occasional case of permanent sterility, Depo-Provera should not be used by women who may wish to have another baby in the future.

I have tried all other kinds of birth control methods and cannot use them or I refuse to use all other kinds of birth control methods. Therefore, I hereby volunteer of my own free will to receive injections of the experimental birth control drug, Depo-Provera, with the full knowledge and understanding that it produced breast tumors and cancer in some dogs and it is not known whether similar tumors or cancers will develop in my breasts.

I understand that I may withdraw from this investigational study of the use of Depo-Provera for contraception at any time.

Signed: ______________________________ ______________
(Patient) (Date)

Witnessed: ______________________________

(Optional on Part of Investigator)

This is to certify that I, ______________________________, husband of ______________________________, hereby agree and consent to have my wife receive injections of the experimental drug, Depo-Provera, every three months. It has been explained to me that my wife may not be able to become pregnant after discontinuing Depo-Provera.

Signed: ______________________________ ______________
(Patient's Husband) (Date)

Witnessed: ______________________________

I have explained to the patient the facts, risks and alternatives contained in the above. She consents to receive Depo-Provera for contraception for the following reason(s) (check one or more):

1. She experienced unacceptable side effects with other methods;
2. She refused to accept the responsibility demanded by other methods;
3. Other methods of contraception have repeatedly failed and further pregnancy is not desired;
4. She prefers Depo-Provera to all other available contraceptive methods.

Signed: ______________________________ ________________
(Physician) (Date)

OCT 12 1972

Dr. Delphis C. Goldberg
Intergovernmental Relations Subcommittee
House Committee on Government Operations
House of Representatives
Washington, D.C. 20515

Dear Dr. Goldberg:

This is in response to the requests made in your October 2 telephone conversation with Mr. Robert Wetherell of this Office regarding Depo-Provera.

Copies of the DESI report and the current labeling for Depo-Provera are enclosed. You may also be interested in the enclosed copy of the July 27, 1972 *Federal Register* announcement on Depo-Provera efficacy.

The new drug application for Depo-Provera was first made effective on November 1, 1960.

Please let us know if we can be of further assistance.

Sincerely yours,

Gerald F. Meyer, Director
Office of Legislative Services

Enclosures
DESI Reports
Repr FR 7/27/72
Depo-Provera label

cc: Congressional Liaison Office
CL-10 (2)
BD-47
R/D:WmDworkin:10/12/72
F/T:HRR:10/12/72

October 2, 1972

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Dr. Delphis Goldberg
Intergovernmental Relations Subcommittee
House Committee on Government Operations

and

Robert C. Wetherell
Deputy Director
Office of Legislative Services

Dr. Goldberg was called in response to his telephone request of September 26 for information on "Colestid" and "Depo-Provera." After giving him the Bureau of Drugs' responses to his earlier questions, Dr. Goldberg asked that he be provided the following information:

1. Copy of DESI report on Depo-Provera for endometriosis.
2. Date the Depo-Provera NDA was approved. — NDA 12-541 — first approved for injection on 9-23-60
3. A copy of the current approved labeling for Depo-Provera.

Robert C. Wetherell

cc: CL-1
CL-10 (2)
BD-1 (FYI)
BD-30 (ACTION)

RCWetherell [illegible] 10/2/72
[illegible] 10/4/72

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL
Division of Medical Sciences

DRUG EFFICACY STUDY

575

Form A
(To be submitted in duplicate by applicant)

E11

2.4

1. NDA Number 12-541 2. Date Originally Approved November 1, 1960 3. Rx ☒ OTC ☐

4. Brand Name Depo-Provera

5. Applicant's Name The Upjohn Company

and Address Kalamazoo, Michigan

6. Quantitative Formula

tablished (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Medroxyprogesterone Acetate	50 mg./cc.

Dosage Form (tablets, etc.) Sterile Aqueous Suspension

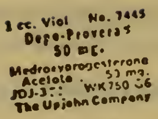
Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Intramuscular

Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

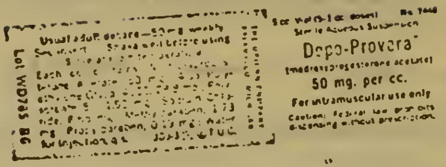
List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).



1 cc. Vial No. 7445
Depo-Provera®
50 mg.
Medroxyprogesterone
Acetate . 50 mg.
JDJ-3 WK750 36
The Upjohn Company



Lot WD7as BG
Usual adult dosage—50 mg weekly
Each cc. contains

See ... 1 cc. ... No. 7445
Sterile Aqueous Suspension
Depo-Provera®
(medroxyprogesterone acetate)
50 mg. per cc.
For intramuscular use only
Caution: Federal law prohibits dispensing without prescription.

Sterile Aqueous Suspension

Depo-Provera®

Upjohn

(medroxyprogesterone acetate)

Medroxyprogesterone acetate, 17α-hydroxy-6α-methylprogesterone acetate, is a highly active progestational agent. Provera® (medroxyprogesterone acetate) is a white to off-white, odorless crystalline powder melting at 200-208° C. It is practically insoluble in water, only slightly soluble in ether, and somewhat soluble in alcohol and chloroform.

Provera (medroxyprogesterone acetate) shows exceptionally high progestational activity when administered in tablet form by mouth or in the form of Depo-Provera (medroxyprogesterone acetate) by intramuscular injection. As with other oral progestational agents the duration of action by mouth is relatively short whereas upon intramuscular injection the duration of action is greatly prolonged (See section "Clinical Studies"). Because of this prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, Depo-Provera (medroxyprogesterone acetate) is not recommended in secondary amenorrhea, or functional uterine bleeding. In these conditions oral therapy is recommended.

Excretion and Metabolism of Progesterone

Progesterone is secreted primarily by the corpus luteum and the placenta. However, only slight biologic activity has been obtained from relatively large amounts of these tissues. This suggests that the hormone is secreted soon after its formation.

In the human being, progesterone is excreted in the form of various derivatives, the inactive steroid alcohol pregnanediol being of particular interest. Urinary excretion studies indicate that approximately 25% of the endogenous progesterone is excreted in the urine as pregnanediol during the luteal non-pregnant state or during pregnancy. In Table I, the amounts of progesterone secreted daily by the human female have been calculated on the basis of pregnanediol excretory data. These data, indicating the large amounts of progesterone secreted, particularly during pregnancy, are in accord with the trend toward the use of increasingly larger doses of progestational agents.[1]

Table I

Amount of Progesterone Secreted per 24 Hours by Human Female

	Urinary pregnanediol excretion In mg./24 hrs.	Progesterone secretion (calculated amount) in mg./24 hrs.
Normal Menstruation Cycle		
Postovulatory phase	10	40
Pregnancy		
First trimester	15	60
Second trimester	40	160
Third trimester	80	320

[1] Provera (medroxyprogesterone acetate) is apparently not excreted as pregnanediol.

Physiologic Activity of Provera

Comparative studies in immature female rabbits employing the McPhail method of assay (endometrial) response indicate that medroxyprogesterone acetate is 24 to 43 times as potent as progesterone when administered by the subcutaneous route. Similarly, comparative studies in ovariectomized rats indicate that subcutaneously administered Provera (medroxyprogesterone acetate) is approximately 25 times as effective as subcutaneously administered progesterone in maintaining pregnancy.

Provera (medroxyprogesterone acetate) is highly active in suppressing ovulation in experimental animals. When injected subcutaneously, it is 20 to 30 times as potent as progesterone in this respect. Comparative studies of the suppression of follicle stimulating hormones (FSH) and luteinizing hormone (LH) in rats indicates, likewise, that medroxyprogesterone acetate is considerably more active than progesterone.

Of particular interest in the studies of investigative animals are those involving androgenic effects of progestational agents. The standard tests for determining the androgenic potency of synthetic hormones are to determine the increases in weight of the seminal vesicles and the prostate in castrated weanling male rats. The results obtained with three progestational agents are shown in Table II.

The estrogenic activity of Provera (medroxyprogesterone acetate) was estimated employing the increase in weight of the uterus of the spayed immature rat as the indicator of activity. On the basis of this test, the estrogenic potency of medroxyprogesterone acetate is approximately 1/10,000 that of estradiol.

Table II

Androgenicity of Progestational Agents

	Oral Administration	
	Seminal Vesicle	Prostate
Ethisterone	3	1**
Progesterone	V.sl*	3
Medroxyprogesterone acetate	V.sl	6

*V.sl = less than 1% of the activity of a standard androgen, methyltestosterone.
**1 is the most potent — 5 is the least potent.

Clinical Studies

The effectiveness of Provera (medroxyprogesterone acetate) in producing secretory changes in the endometrium, withdrawal bleeding, and other progestational effects has been studied in surgical castrates, patients with amenorrhea, functional uterine bleeding and dysmenorrhea.

In a study of the effect upon the endometrium, the drug was administered intramuscularly in 29 artificial cycles in 8 estrogen-primed surgical castrates. A threshold secretory effect was produced by a single injection of 25 mg. and an optimal effect by an injection of 50 mg. A single dose of 50 mg. of Depo-Provera (medroxyprogesterone acetate) injected on the 15th day of the test cycle was found to be equivalent in potency to 10 daily injections of 20 mg. each of progesterone in oil, either dosage schedule producing a complete secretory change. This may be compared also with the doses of 100 mg. of 17α-hydroxyprogesterone caproate on the 15th and 22nd days and a dose of 100 to

150 mg. of 17α ethinyl-19-nortestosterone enanthate on the 15th day which were required to produce a complete secretory effect.

The effect in producing withdrawal bleeding was somewhat variable. Following administration of a single dose of 50 mg. on the 15th day of the cycle, withdrawal bleeding of 3 to 4 days' duration began on the 25th to 41st day, the average time of the onset of bleeding falling on the 31st day, indicating that this dose has a duration of action of approximately 16 days.

In another study, the progestational effects were studied in 18 patients with such conditions as amenorrhea, menorrhagia, and endometriosis, the preparation being administered intramuscularly in doses of 50 to 200 mg. at 7 to 10 day intervals for a period of six months.

Depo-Provera (medroxyprogesterone acetate) was found to be a highly potent, long acting progestational agent. A single intramuscular injection of 50 to 150 mg. resulted in a sharp rise in basal temperature to ovulatory levels within 48 hours, which persisted as long as 50 days. Within 4 days after an injection of 150 mg., the formation of fern-like patterns in dried cervical mucus of amenorrheic and postmenopausal patients, characteristic of the estrogenic phase, was suppressed and was still absent 30 days later. In the vaginal mucosa, a luteal type cytologic smear replaced the estrogenic type within a few days after injection. Progestational changes were also noted in the endometrium. However, administration for prolonged periods produced atrophic changes in the endometrial glands and decidual changes in the stroma, with eventual true atrophy. This indicated an anti-estrogenic effect. During prolonged administration, there were no significant alterations from normal values of urinary 17-ketosteroids or 17-ketogenic steroids. Apparently Provera (medroxyprogesterone acetate) is not metabolized to pregnanediol.

In this study, administration of 50 mg. of Depo-Provera (medroxyprogesterone acetate) at weekly intervals over a period of 6 months or longer, was found to be helpful in the management of patients with endometriosis. Such therapy was accompanied by relief of pelvic pain, absence of menses and general improvement similar to that occurring in pregnancy. In patients with functional uterine bleeding, one or two

injections of 50 to 100 mg. was followed by cessation of bleeding. However, withdrawal bleeding was delayed in onset and the time of onset was difficult to predict.

In these studies, administration of Depo-Provera (medroxyprogesterone acetate) was well tolerated both locally and systemically. There were no estrogenic or androgenic effects even after prolonged administration.

In summary, Depo-Provera (medroxyprogesterone acetate) appears to be a highly specific progestational agent. It is well tolerated both locally and systemically and is apparently devoid of significant estrogenic or androgenic activity. As indicated by its ability to produce a complete secretory endothelium in estrogen-primed surgical castrates, medroxyprogesterone acetate is:

(1) Four times as potent as 17α-hydroxyprogesterone caproate,
(2) Two to three times as potent as 17α-ethinyl-19-nortestosterone enanthate, and
(3) At least four times as potent as progesterone.

Indications

Depo-Provera (medroxyprogesterone acetate) is indicated in habitual and threatened abortion and in endometriosis.

Contraindications

Provera (medroxyprogesterone acetate), administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated. This preparation should not be administered to patients known to be sensitive to it.

Precautions

Studies in animals show that medroxyprogesterone acetate possesses adrenocorticoid activity. A recent study has indicated that medroxyprogesterone acetate is capable of maintaining adrenalectomized patients (100 mg. daily subcutaneously). Repression of adrenocortical function has not been observed in the extensive clinical experience with this agent to date. In one study seven patients received as much as 200 mg. of this agent by mouth daily from one to six months without evidence of suppression. However, patients receiving large doses of medroxyprogesterone acetate continuously for prolonged periods should be observed closely. Large doses of this agent have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Hypercalcemia has been reported following administration of Provera (medroxyprogesterone acetate) in 4 of 20 patients with mammary cancer and X-ray evidence of osseous metastases (R. J. Kaufman et al. Am. Assn. Cancer Res., Proc. 4:33, April, 1963). This was interpreted as indicating a direct tumor stimulating effect. This conclusion has not been confirmed by other investigators. Hypercalcemic episodes are not uncommon in these patients and may occur spontaneously or following administration of sex hormones (Jessiman et al. Ann. Surg. 157:377, 1963). In unpublished studies, other investigators have noted regression of lesions in patients with mammary cancer treated with this agent.

As with any new drug, the advisability of discontinuing therapy for a few weeks should be considered if tests of thyroid function are to be done. To date, there are no data indicating that therapy with medroxyprogesterone acetate affects thyroid function. Subcutaneous administration of the drug to rats in doses of 1 mg./100 g. body weight daily for 65 to 80 days did not result in change in thyroid function as indicated by I131 uptake, histologic appearance or weight of the gland (Kracer and Logothetopoulos, Endo. 71:660, October, 1962). Daily oral administration of this drug in doses of 5 mg. for 20 days to euthyroid men produced no change in protein bound iodine or red cell take-up of triiodothyronine (Hollander et al. New Eng. J. Med. 269:501, 1963). Carter et al. (in "Biological Activities of Steroids in Relation to Cancer", Academic Press, New York, 1960, pp. 77-89) observed no change in levels of serum PBI in five postmenopausal women receiving from 40 to 200 mg. of medroxyprogesterone acetate daily by mouth.

A number of agents including estrogens and androgens are known to be capable of altering values for protein bound iodine. Increases in protein bound iodine have been reported to occur following administration of norethynodrel compound (norethynodrel with ethinyl estradiol, methyl ether; Hollander et al. loc. cit.) and in an obstetric patient receiving norethindrone and conjugated estrogens (Sherer, Med. Am. D. C. 30:77, 1961). In the absence of definitive studies concerning the effect of these progestational agents on thyroid function, it appears that the reported effect may have been due to estrogen.

Side Effects

Intramuscular injections have been well tolerated. There has been little or no pain at the site of injection. Sensitivity reactions ranging from urticaria to anaphylaxis have been reported in an occasional patient following intramuscular injection of this preparation. Mild alopecia and hirsutism have been reported in a few cases.

As indicated under "Clinical Studies," because of the prolonged effect of intramuscular injection of this suspension, withdrawal bleeding following such administration may be delayed in onset and difficult to predict. Thus, following repeated injections for endometriosis, menstruation may not be re-established for several months. There is evidence indicating that this prolonged effect may be greater with subcutaneous than with intramuscular administration.

Dosage and Administration

The suspension is intended for intramuscular administration only.

Habitual and Threatened Abortion—While the etiology of habitual and threatened abortion is incompletely understood, excretion studies have indicated that deficiency of endogenous progesterone may be an important factor. For this reason, progesterone replacement therapy is recommended in the management of these conditions. Recent clinical reports reflect a trend toward increasingly higher doses of progestational agents for this purpose. The recommended doses of Depo-Provera (medroxyprogesterone acetate) in these conditions are as follows:

Habitual Abortion:

First trimester	50 mg. every week
Second trimester	100 mg. every two weeks
Third trimester	100 mg. every two weeks through the eighth month

Threatened Abortion:

50 mg. daily when symptoms are present, followed by 50 mg. weekly through the first trimester, or until fetal viability is evident.

Therapy with medroxyprogesterone acetate should be employed in addition to other accepted measures of management.

Endometriosis—In recent years progestational agents have been employed alone or in combination with estrogens in the treatment of endometriosis. This treatment is based upon the well-known beneficial effect of pregnancy in this condition. Recent reports indicate that satisfactory results may be obtained in approximately 85% of the patients treated. More data will be required, however, to determine the permanence of such beneficial effects.

The recommended dose of Depo-Provera (medroxyprogesterone acetate) in this condition is 50 mg. weekly or 100 mg. every two weeks for at least six months.

The Package

Sterile Aqueous Suspension Depo-Provera (medroxyprogesterone acetate) 50 mg./cc. is supplied in 1 cc. and 5 cc. vials.

Each cc. contains:

Medroxyprogesterone Acetate	50 mg.
Polyethylene Glycol 4000	28.8 mg.
Polysorbate 80	1.92 mg.
Sodium Chloride	8.65 mg.
Methylparaben	1.73 mg.
Propylparaben	0.19 mg.
Water for Injection	q.s.

The Upjohn Company • Kalamazoo, Michigan JDI-5

June 1965

Depo-Provera
(medroxyprogesterone acetate)

Page 1 of 1

DEPO-PROVERA
NDA 12541
LOG 575

Panel on Drugs Used in Disturbances of the Reproductive System

INDICATIONS

I. Habitual and threatened abortion.

EVALUATION: Probably effective.

COMMENTS: The literature is contrasting on the usefulness of progestogens in these indications. Some of the studies are quite optimistic, but the Panel believes that more definitive studies should be encouraged to help clarify the role of such therapy. Because efficacy has not been proved, additional documentation should be supplied by the manufacturer within a reasonable period.

DOCUMENTATION:

1. Allen, W. M. The use of progestational agents in pregnancy. Rocky Mountain Med. J. 62:31-35, 1965.
2. Davis, M. E., and E. J. Plotz. The metabolism of progesterone and its clinical use in pregnancies. Recent Progr. Hormone Res. 13:347-388, 1957.
3. Goldzieher, J. W. Double-blind trial of a progestin in habitual abortion. J.A.M.A. 188:651-654, 1964.
4. Wurm, R. Experience with medroxy-progesterone acetate in the control of threatened late abortion and premature labour. Aust. New Zeal. J. Obstet. Gynaec. 3:145-154, 1963.

II. Endometriosis.

EVALUATION: Effective.

COMMENTS: None.

DOCUMENTATION:

1. Kistner, R. W. Current status of the hormonal treatment of endometriosis. Clin. Obstet. Gynec. 9:271-292, 1966.
2. Kupperman, H. S. Endometriosis. GP 25:86-90, 1962.

Approved by
Chairman

[DESI 11839]

MEDROXYPROGESTERONE ACETATE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs containing medroxyprogesterone acetate.

Provera tablets; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49001 (NDA 11-839).

Depo-Provera Sterile Aqueous Suspension; The Upjohn Co. (NDA 12-541).

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). The effectiveness classification and marketing status are described below.

A. Effectiveness classification. The Food and Drug Administration has considered the Academy's reports, as well as other available evidence, and concludes that:

1. Medroxyprogesterone acetate administered orally is:

a. Effective for secondary amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; and as a presumptive test for pregnancy.

b. Probably effective for habitual and threatened abortion.

c. Possibly effective for infertility, premenstrual tension, and dysmenorrhea.

2. Medroxyprogesterone acetate administered intramuscularly is:

a. Probably effective for endometriosis.

b. Lacking substantial evidence of effectiveness for threatened and habitual abortion.

B. Conditions for approval and marketing of drug having an effective indication. The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* Medroxyprogesterone acetate preparations are in tablet form suitable for oral administration.

2. *Labeling conditions.* a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the Act and regulations and the labeling bears adequate information for safe and effective use of the drug. The effective and probably effective indications are as follows:

This drug is indicated in secondary amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer, as a presumptive test for pregnancy; and for habitual and threatened abortion.

(The possibly effective indications may also be included for 6 months.)

3. *Marketing status.* Marketing of such drugs may be continued under the conditions described in the notice entitled "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), as follows:

a. For holders of "deemed approved" new drug applications (i.e., an application which became effective on the basis of safety prior to October 10, 1962), the submission of a supplement for revised labeling and an abbreviated supplement for updating information as described in paragraphs (a)(1) (i) and (iii) of the notice of July 14, 1970.

b. For any person who does not hold an approved or effective new drug application, the submission of an abbreviated new drug application as described in paragraph (a)(3)(i) of that notice.

c. For any distributor of the drug, the use of labeling in accord with this announcement for any such drug shipped within the jurisdiction of the Act as described in paragraph (b) of that notice.

d. For indications for which the drug has been classified as probably effective (included in the "Indications" section above) and possibly effective (not included in the "Indications" section above), continued use as described in paragraphs (c), (d), (e), and (f) of that notice.

C. Marketing status of drug having no effective indication. 1. Within 60 days of the date of publication of this announcement in the FEDERAL REGISTER, the holder of any previously approved new-drug application for a drug which is classified in paragraph A above as lacking substantial evidence of effectiveness is requested to submit a supplement to his application, as needed, to provide for revised labeling which deletes those indications for which substantial evidence of effectiveness is lacking and which contains an "Indications" section in accord with that described below. Such supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9 (d) and (e)) which permit certain changes to be put into effect at the earliest possible time, and the revised labeling should be put into use within the 60-day period. Failure to do so may result in a proposal to withdraw approval of the new-drug application.

2. If any such preparation is on the market without an approved new-drug application, its labeling should be revised to delete all claims for which substantial evidence of effectiveness is lacking as described in paragraph A above and to be in accord with this notice. Failure to delete such indications and to put the revised labeling into use within 60 days after the date of publication hereof in the FEDERAL REGISTER may cause the drug to be subject to regulatory proceedings.

3. Labeling revised pursuant to this notice should take into account the comments of the Academy; furnish adequate information for safe and effective use of the drug; and recommend use of the drug for the probably effective indications as follows:

INDICATIONS

This drug is indicated for endometriosis.

The notice "Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study," published in the FEDERAL REGISTER July 14, 1970 (35 F.R. 11273), describes in paragraphs (c), (e), and (f) the marketing status of the drug labeled with those indications for which it is regarded as probably effective.

A copy of the Academy's report has been furnished to the firm referred to above. Communications forwarded in response to this announcement should be identified with the reference number DESI 11839, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (identify with NDA number): Office of Scientific Evaluation (BD-100), Bureau of Drugs.

Original abbreviated new-drug applications (identify as such): Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

Requests for the Academy's report: Drug Efficacy Study Information Control (BD-67), Bureau of Drugs.

All other communications regarding this announcement: Drug Efficacy Study Implementation Project Office (BD-60), Bureau of Drugs.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 10, 1972.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.72-11613 Filed 7-26-72;8:50 am]

15033

Upjohn

Sterile Aqueous Suspension

Depo-Provera®

(Sterile Medroxyprogesterone Acetate Suspension, U.S.P.)

DESCRIPTION

Medroxyprogesterone acetate, U.S.P. is a derivative of progesterone and is active by the parenteral and oral routes of administration. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200 and 210° C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether and insoluble in water.

ACTIONS

Depo-Provera (medroxyprogesterone acetate) administered parenterally in the recommended doses to women with adequate endogenous estrogen transforms proliferative endometrium into secretory endometrium.

Depo-Provera inhibits (in the usual dose range) the secretion of pituitary gonadotropin which, in turn, prevents follicular maturation and ovulation.

Because of its prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, Depo-Provera is not recommended in secondary amenorrhea or dysfunctional uterine bleeding. In these conditions oral therapy is recommended.

INDICATIONS

Depo-Provera (medroxyprogesterone acetate) is indicated in endometriosis and as adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial carcinoma.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions.
2. Markedly impaired liver function.
3. Carcinoma of the breast.
4. Undiagnosed vaginal bleeding.
5. Missed abortion.
6. Known sensitivity to Depo-Provera (medroxyprogesterone acetate).

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.
2. Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug treated animals were larger, more numerous, persistent, and there were

Depo-Provera
(medroxyprogesterone
acetate)
(Code)

some breast malignancies with metastases. Their significance with respect to humans has not been established.

3. The use of Depo-Provera (medroxyprogesterone acetate) for contraception is investigational since there are unresolved questions relating to its safety for this indication. Therefore, this is not an approved indication for this use.
4. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.
5. Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing infant has not been determined.
6. Masculinization of the female fetus has occurred when progestins have been used in pregnant women.
7. Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives. There have been three principal studies in Great Britain[1-3] leading to this conclusion, and one[4] in this country. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about sevenfold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products.

References

1. Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. J. Coll. Gen. Pract., 13:267-279, 1967.
2. Inman, W. H. W. and Vessey, M. P., Investigation of Deaths from Pulmonary Coronary and Cerebral Thrombosis and Embolism in Women in Child-Bearing Age, Brit. Med. J., 2:193-199, 1968.
3. Vessey, M. P. and Doll, R., Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit. Med. J., 2:651-657, 1969.
4. Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study, Am. J. Epidem., 90:365-380, (Nov.) 1969.

8. Following repeated injections, amenorrhea and infertility may persist for periods up to 18 months and occasionally longer.

PRECAUTIONS

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.
2. Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
3. In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.
4. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

5. Any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic or uterine functions awaits further study.
6. A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.
7. The pathologist should be advised of progestin therapy when relevant specimens are submitted.
8. Because of the occasional occurrence of thrombotic disorders, (thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations and since the mechanism is obscure, the physician should be alert to the earliest manifestation of these disorders.

ADVERSE REACTIONS

In a few instances there have been undesirable sequelae at the site of injection, such as residual lump, change in color of skin or sterile abscess.

The following adverse reactions have been associated with the use of Depo-Provera (medroxyprogesterone acetate).

Breast—In a few instances, breast tenderness or galactorrhea have occurred.

Pregnancy—A few cases of clitoral hypertrophy have been reported in newborn females, whose mothers received Depo-Provera during pregnancy. Prolonged postpartum bleeding, postabortal bleeding and missed abortion have been reported.

Psychic—An occasional patient has experienced nervousness, insomnia, somnolence, fatigue or dizziness.

Thromboembolic Phenomena—Thromboembolic phenomena including thrombophlebitis and pulmonary embolism have been reported.

Skin and Mucous Membranes—Sensitivity reactions ranging from pruritus, urticaria, angioneurotic edema to generalized rash and anaphylaxis have occasionally been reported. Acne, alopecia, or hirsutism have been reported in a few cases.

Gastrointestinal—Rarely, nausea has been reported. Jaundice, including neonatal jaundice, has been noted in a few instances.

Miscellaneous—Rare cases of headache and hyperpyrexia have been reported.

The following adverse reactions have been observed in women taking progestins including Depo-Provera:

breakthrough bleeding
spotting
change in menstrual flow
amenorrhea
edema
change in weight (increase or decrease)
changes in cervical erosion and cervical secretions
cholestatic jaundice
rash (allergic) with and without pruritus
melasma or chloasma
mental depression

A statistically significant association has been demonstrated between use of estrogen-progestin combination drugs and the following serious adverse reactions: thrombophlebitis; pulmonary embolism and cerebral thrombosis and embolism. For this reason patients on progestin therapy should be carefully observed.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs:

rise in blood pressure in susceptible individuals
premenstrual-like syndrome
changes in libido
changes in appetite
cystitis-like syndrome
headache
nervousness
dizziness
fatigue
backache
hirsutism
loss of scalp hair
erythema multiforme
erythema nodosum
hemorrhagic eruption
itching

In view of these observations, patients on progestin therapy should be carefully observed.

Female fetal masculinization has been observed in patients receiving progestins.

DOSAGE AND ADMINISTRATION

The suspension is intended for intramuscular administration only.

Endometriosis—The recommended dose of Depo-Provera (medroxyprogesterone acetate) in this condition is 50 mg weekly or 100 mg every two weeks for at least six months.

Endometrial carcinoma—doses of 400 mg to 1000 mg of Depo-Provera per week are recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month. Medroxyprogesterone acetate is not recommended as primary therapy, but as adjunctive and palliative treatment in advanced inoperable cases including those with recurrent or metastatic disease.

HOW SUPPLIED

Sterile Aqueous Suspension Depo-Provera (medroxyprogesterone acetate) 50 mg per ml and 100 mg per ml are available in 1 ml and 5 ml vials.

50 mg/ml	**Each ml contains:**	**100 mg/ml**
50 mg	Medroxyprogesterone Acetate	100 mg
	Also	
28.8 mg	Polyethylene Glycol 4000	27.6 mg
1.92 mg	Polysorbate 80	1.84 mg
8.65 mg	Sodium Chloride	8.3 mg
1.73 mg	Methylparaben	1.65 mg
0.19 mg	Propylparaben	0.18 mg
qs	Water for Injection	qs

When necessary pH was adjusted with sodium hydroxide and/or hydrochloric acid.

Sterile Aqueous Suspension Depo-Provera 400 mg/ml is available in 2.5 and 10 ml vials and 1 ml disposable syringes.

Each ml contains:	
Medroxyprogesterone Acetate	400 mg
Polyethylene Glycol 4000	20.3 mg
Sodium Sulfate Anhydrous	11 mg
Myristyl-gamma-picolinium Chloride	1.7 mg
Water for Injection	qs

Caution: Federal law prohibits dispensing without prescription.

The Upjohn Company • Kalamazoo, Michigan 49001, U.S.A. (code)
June 1972

Original Informed
Consent.

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

1HD-1
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3/9/

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001
TELEPHONE (616) 382-4000

FERTILITY RESEARCH
Office of
PAUL C. SCHWALLIE, M.D.
Chief

February 25, 1972

Dear Doctor:

The Federal Food and Drug Administration has directed us to send to you the enclosed patient consent forms. The Spanish version of the consent form is to be used for Spanish-speaking patients. Each patient or her parent(s) or guardian must sign the form before she may enter or continue to participate in the Depo-Provera contraceptive study in which you are the investigator. One copy must be retained in your files and one copy must be sent to The Upjohn Company, 301 Henrietta Street, Kalamazoo, Michigan 49001 (Attention Dr. P. C. Schwallie).

According to our records, you now have _____ patients participating in your study. We are enclosing _____ sets of each of the English and Spanish versions of the form for this number of patients plus _____ sets for additional patients. If you need more sets of forms, please advise me.

Sincerely,

Paul C. Schwallie, M. D.

PCS:lav

Enclosures

VS-1945 1/72

Depo-Provera Written Informed Consent Form for Contraceptive Studies

This is to certify that I, ____, hereby agree and consent to receive an injection of an experimental drug called Depo-Provera every three months under the care and supervision of Dr. ______________________________________. I understand that this injection will be given to me in an attempt to keep me from becoming pregnant. I have been told that tests in dogs injected with this drug showed that some of them developed tumors in their breasts. Some of these tumors may be cancer or may develop into cancer. It is not known whether or not similar tumors will grow in my breasts after receiving the drug.

It has been explained to me that there are available other non-experimental methods of preventing pregnancy such as pills, vaginal creams, jellies, foams, diaphragms, various devices which are inserted into my womb and use of a rubber (condom) by my husband. The effectiveness of these various methods of contraception, as well as the advantages and disadvantages of each method, has been explained to me. Surgical sterilization of myself or my husband (along with its risks, advantages and disadvantages) has been explained to me as a nonreversible method of contraception. I have also been told of the effectiveness of Depo-Provera.

I have read and understand the pamphlet prepared by the American Medical Association, American College of Obstetricians and Gynecologists and the Food and Drug Administration informing users of the pill about the possible problems which a woman may encounter during its use. I understand also that Depo-Provera is similar to the pill in that I may have some of the same problems occurring that are mentioned in the pamphlet such as blood clots, tender breasts, nausea, vomiting, weight gain, weight loss, spotty darkening of the skin of the face, mental depression, elevated levels of sugar and fatty substances in the blood, dizziness, loss of hair, increase in body hair and increased or decreased sex drive.

It has been explained to me that it is quite likely that I will have unexpected vaginal bleeding, completely irregular menstrual cycles or no menstrual bleeding at all as a result of the Depo-Provera injections. I also understand that the injections may have some effect on the amount of estrogenic and adrenal hormones produced in my body and that the importance of these changes is still being investigated.

I understand, also, that after a woman stops taking Depo-Provera there may be an unpredictable and prolonged delay before she is able to become pregnant or may be unable to become pregnant at all. Because of the possibility of an occasional case of permanent sterility, Depo-Provera should not be used by women who may wish to have another baby in the future.

Formulario de Informe y Consentimiento por Escrito para Estudios con Depo-Provera como Anticoncepcional

IND

92-006 2/72

3/

La presente es para certificar que la que suscribe, ____, está de acuerdo y consiente en recibir cada tres meses, una inyección de un medicamento experimental denominado Depo-Provera, bajo la vigilancia y supervisión del Dr. ____. Entiendo que se me administrará esta inyección con la intención de evitar de que yo quede embarazada. Se me ha informado que los ensayos en perras inyectadas con éste medicamento revelaron que algunas de ellas desarrollaron tumores en las mamas. Algunos de estos tumores pueden ser cancerosos o pueden transformarse en cancerosos. No se sabe si se desarrollarán o no tumores similares en mis mamas después de recibir el medicamento.

Se me ha explicado que existen otros métodos no experimentales para evitar el embarazo tales como píldoras, cremas, jaleas, espumas, diafragmas vaginales, diferentes dispositivos que se insertan en mi matriz y el uso de preservativos (condón) por mi esposo. Se me explicó la eficacia de estos diversos métodos anticoncepcionales, como también las ventajas y desventajas de cada método. Se me explicó la esterilización quirúrgica tanto para mí como para mi esposo (junto con sus riesgos, ventajas y desventajas) como un método anticoncepcional irreversible. También se me habló de la eficacia de Depo-Provera.

He leído y entendido el folleto preparado por la Asociación Médica Americana, Colegio Americano de Obstetras y Ginecólogos y Administración de Drogas y Alimentos, donde se informa a las que usan la píldora sobre los posibles problemas que puede encontrar una mujer durante su uso. Entiendo tambien que Depo-Provera es similar a la píldora en cuanto a que yo puedo tener algunos de los mismos problemas que ocurren y que se mencionan en el folleto, tales como coágulos sanguíneos, dolor de las mamas a la palpación, náuseas, vómitos, aumento de peso, pérdida de peso, oscurecimiento en diferentes zonas de la piel de la cara, depresión mental, concentraciones el[illegible]azúcar y substancias grasas en la sangre, mareos, pérdida del cabello, aumento del vello en el cuer[illegible]ento o disminución del deseo sexual.

IRB-1
6
3/9/

I have tried all other kinds of birth control methods and cannot use them or I refuse to use all other kinds of birth control methods. Therefore, I hereby volunteer of my own free will to receive injections of the experimental birth control drug, Depo-Provera, with the full knowledge and understanding that it produced breast tumors in some dogs and it is not known whether similar tumors will develop in my breasts.

I understand that I may withdraw from this investigational study of the use of Depo-Provera for contraception at any time.

Signed: ______________________ (PATIENT) ____________ (DATE)

Witnessed: ______________________

(Optional on Part of Investigator)

This is to certify that I, ______________________, husband of ______________________, hereby agree and consent to have my wife receive injections of the experimental drug, Depo-Provera, every three months. It has been explained to me that my wife may not be able to become pregnant after discontinuing Depo-Provera.

Signed: ______________________ (PATIENT'S HUSBAND) ____________ (DATE)

Witnessed: ______________________

I have explained to the patient the facts, risks and alternatives contained in the above. She consents to receive Depo-Provera for contraception for the following reason(s) (check one or more):

1. She experienced unacceptable side effects with other methods;
2. She refused to accept the responsibility demanded by other methods;
3. Other methods of contraception have repeatedly failed and further pregnancy is not desired;
4. She prefers Depo-Provera to all other available contraceptive methods.

Signed: ______________________ (PHYSICIAN) ____________ (DATE)

IND-1036
3
3/9/72

Se me ha explicado que es muy posible que yo pueda tener sangrado vaginal inesperado, ciclos menstruales completamente irregulares o ningún sangrado menstrual como resultado de las inyecciones de Depo-Provera. También entiendo que las inyecciones pueden tener algún efecto sobre la cantidad de hormonas estrogénicas y adrenales producidas por mi organismo y que aún se está investigando la importancia que puedan tener dichos cambios.

También entiendo que después que una mujer deja de recibir Depo-Provera, puede haber una demora prolongada y no pronosticable antes de que ella pueda quedar embarazada o que en definitiva no pueda quedar embarazada. Debido a la posibilidad de que se puedan producir casos de esterilidad permanente, Depo-Provera no deberá ser usado por mujeres que puedan desear otro hijo en el futuro.

Yo he probado todas las otras clases de métodos de control de la natalidad y no los puedo usar o rehuso a usar todos los demás tipos de métodos de control de la natalidad. Por lo tanto, yo aquí declaro que por mi propia y libre voluntad me presto a recibir inyecciones del medicamento experimental para el control de la natalidad, Depo-Provera, con completo conocimiento y entendimiento que el mismo ha producido tumores en las mamas de algunas perras y que no se sabe si se desarrollarán tumores similares en mis mamas.

Entiendo que en cualquier momento puedo retirarme de este estudio de investigación sobre el uso de Depo-Provera para la anticoncepción.

Firmado: ______________________ ______________________
(Paciente) *(Fecha)*

Testigo: ____

–3–

(Opcional por parte del Investigador)

La presente es para certificar que yo, ____

esposo de ____, aquí declaro que estoy conforme y consiento que mi esposa reciba cada tres meses inyecciones del medicamento experimental, Depo-Provera. Se me ha explicado que podría ocurrir que mi esposa no pueda quedar embarazada después de suspender el tratamiento con Depo-Provera.

Firmado: ______________________________ ____________________
(esposo de la paciente) (fecha)

Testigo: ____

He explicado a la paciente los hechos, riesgos y alternativas que se describen anteriormente. Ella
ente en recibir Depo-Provera con fines anticoncepcionales por la(s) siguiente(s) razón(es) (marcar una o más):
en otros métodos ella ha experimentado efectos secundarios intolerables;
la ha rehusado a aceptar la responsabilidad que exigen otros métodos;
los métodos anticoncepcionales han fracasado repetidamente y no desea ningún otro embarazo;
la prefiere Depo-Provera sobre todos los otros métodos anticocepcionales disponibles.

Firmado: ______________________________ ____________________
(Médico) (fecha)

DEPARTMENT OF HEALTH, EDUCATION, AND
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

September 25, 1972

Request for Proposals RFP-CPR-73-4

Contract Program for Clinical Studies of Estrogens as Postcoital Contraceptive Agents

The Center for Population Research of the National Institute of Child Health and Human Development is issuing its first Request for Proposals in the Center's program to determine the safety and efficacy of estrogens as postcoital contraceptive agents.

The aims and requirements of this request are described in the following sections:

I. Contract Program for the establishment of the safety and efficacy of estrogens as postcoital contraceptive agents.
II. Content and Format of Proposals.
III. Method and Criteria for Review of Proposals.
IV. Administrative Certifications and Legal Requirements.

Forty copies of proposals submitted in response to this RFP must be received at the address immediately below by 5:00 p.m., local time, on November 25, 1972. Proposals should be addressed to:

Contracting Officer
Grants and Contracts Management Branch
National Institute of Child Health and
Human Development
Building 31, Room 3A-22
Bethesda, Maryland 20014

If you have questions about the program, please do not hesitate to telephone. Questions concerning scientific aspects of the program should be directed to Richard P. Blye, Ph.D., Contraceptive Development Branch, Center for Population Research; the telephone number is (301) 496-1661. Questions concerning administrative and fiscal matters should be directed to Mr. Paul J. Duska, Contracts Management Section, Grants and Contracts Management Branch, NICHD; his telephone number is (301) 496-4611.

We hope that this RFP and participation in the program are of interest to you.

Philip A. Corfman, M.D.
Director
Center for Population Research
National Institute of Child Health
and Human Development

Lewis S. Pollack
Lewis S. Pollack
Contracting Officer
Grants and Contracts Management Branc
National Institute of Child Health
and Human Development

Attachments: HEW-315 (rev. 8-64)
HEW-316 (rev. 3-72)

RFP-CPR-73-4

Efficacy and Safety of Estrogens as Postcoital Contraceptive Agents

I. Contract Program for the Establishment of the Safety and Efficacy of Estrogens as postcoital Contraceptive Agents.

A. Program Objectives:

The ability of estrogens to prevent pregnancy in experimental animals has been known for over four decades yet relatively little information is available at the Clinical level in this guise. Recent reports indicate that certain estrogenic substances may be effective in preventing human pregnancy when administered shortly after unprotected midcycle exposure.

As part of its broad interest in methods of fertility control, the Center for Population Research wishes to evaluate the clinical safety and postcoital contraceptive effectiveness of steroidal estrogens presently marketed in the United States. It is the purpose of this RFP to generate sufficient data to support or deny indication for this use. In the event that adequate clinical data can be accumulated supporting the use of specific estrogens as postcoital contraceptives, the Center may file a New Drug Application (NDA) with the Food and Drug Administration (FDA) requesting a label change to include indications for the new use.

B. Program Specifications:

1. Format

Clinical protocols should be essentially "Phase 3" in nature, utilizing large numbers of subjects and designed to show proof of efficacy with careful monitoring for side effects and any idosyncratic drug reactions.

Even though a physician, operating under the rules of the state of his licensure, may employ a marketed durg for both approved (indicated) and other (not indicated) use in his practice, "notice of claimed investigational exemption" (more commonly known as a IND) should be filed for the study of a marketed drug for an unapproved use. An IND should be filed to undertake the study of estrogens as postcoital contraceptive agents inasmuch as this use is not indicated for any estrogen marketed in the United States. Responders to this program should hold or present evidence for the application of an IND for each drug proposed for study.

2. Candidate Estrogens

Candidate compounds must be steroidal estrogens presently marketed in the United States and for which the respondent has obtained or has submitted application for the appropriate IND to undertake the proposed clinical trials. The Center is particulary interested in ethynyl estradiol and conjugated estrogens because their potential clinical utility as post-coital contraceptive agents has already been identified. Respondents proposing the study of other estrogens meeting the aforementioned criteria (steroidal, presently marketed in the U.S.) must present convincing evidence for their selection.

In general, the compound(s) selected should be orally active. Compounds proposed for parenteral administration must be accompanied by human metabolic data showing absorption and excretion rates as well as half life. Long acting estrogens which require more than 24 hours to reach maximum circulatory levels and/or whose activity persists for more than 1 week are considered unacceptable.

3. Subjects

a. General:

A description of the subject population available to the investigator for his proposed studies should be provided as requested under Section I-C of the RFP. Include the total number of subjects anticipated for inclusion in the study during the contract period.

b. Informed Consent:

Informed consent must be obtained for all patients in accordance with HEW guidelines obtainable from: National Institutes of Health, Division of Research Grants Institutional Relations Branch, Westwood Bldg., Room 422, Bethesda, Maryland 20014.

Because the proposed investigation will essentially be a Phase 3 clinical trial, it is the responsibility of the investigator, taking into consideration the physical and mental state of the subject, to decide when it is necessary or preferrable to obtain consent in other than written form. When verbal consent is obtained, it should be so recorded in the medical record of the person receiving the drug.

c. Patient Selection, History and Identifications:

A short medical history of each subject will be obtained prior to inclusion in the study. Physical and gynecological data should be recorded. Subjects with a history of neoplasia of the reproductive tract, breast, gonad or pituitary or whose medical record would, in the opinion of the investigator, otherwise contraindicate the use of estrogens, shall be excluded from the study. Subjects should be identified in such a manner to ensure that no subject enters the study (i.e., is treated) more than once. NO INDIVDUAL SUBJECTS WILL BE GIVEN THE COURSE OF TREATMENT MORE THAN ONCE. Subjects who have previously received estrogens postcoitally for the prevention of pregnancy will be excluded from the study. Every effort will be made to exclude pregnant subjects from the study. To ensure this exemption, each subject will be given a pregnancy test prior to inclusion in the trial. Subjects having positive, marginal or any pregnancy test result other than negative will be excluded from the study.

The proposal will be limited to a study of estrogen medication following a single unprotected midcycle (coital) exposure. Subjects reporting multiple unprotected exposure shall be excluded from the study for that menstrual cycle during which multiple unprotected exposure occurred. Additionally, the following conditions will apply;

(1) The patient must report for medication within 72 hours of exposure.

(2) Orally active estrogens must be administered within 72 hours of unprotected exposure.

(3) The maximum interval between unprotected exposure and the institution of parenteral estrogen medication will depend on the metabolic characteristics of the estrogen proposed for study. In no case will this interval be greater than 72 hours.

(4) Every attempt will be made to see that patients receive the entire course of medication.

(5) Every subject admitted for therapy will be told to refrain from coital exposure during the remainder of menstrual cycle of treatment. Information currently available indicates that while estrogen administration may be effective in preventing pregnancy when instituted shortly after unprotected midcycle exposure, this medication is not contraceptive for subsequent exposure during the remainder of the cycle.

d. Controls:

Neither untreated nor placebo control groups shall be incorporated into the study.

While controls shall not be made a part of the proposed investigation, the Center is interested in acquiring information on the outcome of patients (who have had a single unprotected midcycle exposure) who elect measures other than postcoital contraceptive medication. Respondents whose practice normally includes such patients are urged to include the collection of appropriate data as part of their proposal.

e. Follow-up:

Investigators will undertake careful follow-up procedures to ensure accurate reporting of side effects both during and following medication. Particular attention should be paid to the following:

- Nausea, degree and duration
- Vomiting, duration
- Headache
- Dizziness
- Diarrhea
- Water balance
- Cutaneous reactions
- Breast tenderness
- Vaginal bleeding, degree and duration
- Abdominal cramps

The above list of side effects is by no means complete and investigators should indicate the full extent (and method) of their subject interview in this regard. The onset and duration of menstruation following treatment should be recorded as well as any deviation from the normal bleeding pattern. Prevention of pregnancy during the medicated cycle will be adequately documented by performing a pregnancy test no sooner than 20 days (depending on the sensitivity of the test) nor later than 60 days following the midcycle exposure for which treatment was instituted.

Termination of pregnancy in the event of apparent treatment failure is not supportable under this RFP. However, investigators are requested to indicate the course of action that will be taken in those instances where pregnancy ensues.

4. Reports:

A record for each subject in the program will be prepared according to the outline contained in Exhibit I. These will be summarized at 3 month intervals and reported to the Project Officer. A cumulative review of the program should be established to provide continuous monitoring of the program for untoward side effects and regimen efficacy. Unusual problems should be communicated to the Project Officer directly.

C. Technical Instructions:

Responders are requested to provide the information outlined below in a clear and concise manner.

1. Format

Provide a summary of the investigation proposed including bibliographic references where appropriate.

2. Candidate Estrogens

The following information regarding the estrogens proposed for study must be provided:

a. Generic and trade name
b. Source (manufacturer)
c. Type of formulation, i.e. tablet, capsule, solution, etc.
d. Dose, i.e. quantity of estrogen per tablet, capsule, etc.
e. Compound(s) proposed for parenteral administration must be accompanied by human metabolic data showing absorption and excretion rates as well as half-life. Injected or oral estrogens which require more than 24 hours to reach maximum circulatory levels and/or whose activity persists for more than one week are considered unacceptable.

f. Data showing the potency of the proposed estrogen(s) in terms of human replacement therapy.

3. Notice of Claimed Investigational Exemption for a New Drug

Respondents must supply the following:

a. Where an IND for the proposed use has already been obtained, a copy of the letter from the responsible officer of the Food and Drug Administration (FDA) indicating such approval and identifying the IND number assigned.

b. Where an IND for the proposed use has not been obtained, a copy of the letter to FDA requesting the claimed investigational exemption including correspondence indicating the manufacturer's willingness to provide access to their NDA documents on file with FDA.

c. A statement from the manufacturing company indicating willingness to supply the dosage form of the drug proposed for study.

4. Subjects

a. Describe the subject population available.

b. Estimate the total number of subjects to be studied during the contract period. Responders should have a subject population available sufficient to study a minimum of 200 cases for each drug. Proposals providing for less than 200 cases during the contract period are unacceptable.

c. Provide a copy of the informed consent form which will be used.

d. Provide a copy of the form to be utilized for recording the medical history and examination of each subject and a brief description of the methods employed to obtain this information.

e. Indicate the manner of patient identification.

f. Describe the procedures to be used to eliminate pregnant subjects from the study.

5. Protocol

a. Include the following statement in the proposal: "Neither untreated nor placebo control subjects will be utilized in the proposed investigation."

b. Provide the name of the estrogen, the dosage, and the frequency, duration and route of administration proposed for study.

c. In all proposals employing self medication (i.e. tablets, etc.), indicate the procedures to be followed in the event of "missed" medication (i.e. forgot to take a tablet, tablet lost, vomited, etc.)

d. Respondents will provide adequate justification for the use of estrogens other than those identified above, proposed for study. Human clinical data are preferred. Where the estrogen proposed has not previously been studied as a postcoital contraceptive agent in man, convincing evidence for this use must be provided.

6. Follow-up:

   a. Indicate the follow-up procedure to be employed, including the manner in which data on side effects, onset and duration of menstruation, and pregnancy will be obtained.

      Identify the pregnancy test (include trade name) to be employed and the sensitivity of the test with respect to its proposed use. Thus a pregnancy test whose sensitivity precludes the detection of gestation earlier than 8 weeks following the last menses (approx. 6th week of pregnancy) cannot be employed, for example, 4 weeks after mid cycle exposure.

   b. Include a list of side effects to be monitored.

7. Reports:

   a. Use the format contained in Exhibit I for patient records.

   b. Indicate the manner in which data will be summarized.

8. Clinical Format:

   Submit 40 separately bound copies of the proposed research according to the format in Exhibit II. The narrative portion of the clinical format (Exhibit II) should be organized as follows using, wherever possible, simple language which the layman can understand.

   Purpose of Project:

   Define the scientific basis for the project in a clear and concise manner and provide a statement weighing the risks of treatment against benefits to the subjects.

   Project Protocol:

   (1) A description of the subject population available and the method by which patients will be selected for (and the basis for their exclusion from) the study. Use the guidelines provided in Section I, B,3,C (Patient Selection, History and Identification) of this RFP.

   (2) State that:

      (a) "No individual subject will receive the course of treatment described herein more than once under the terms of this contract."

8.

(b) "Neither untreated nor placebo control subjects will be utilized in the proposed investigation."

(3) Provide a clear and concise description of the research protocol proposed including the name of the estrogen, the dosage, and the frequency, duration and route of administration.

(4) Identify the source of the estrogen.

(5) Indicate the maximum indicated dosages (for estrogen therapy) from the manufacturer's product information and from the medical literature to support the safety of the proposed regimen.

(6) Give IND number or application for the IND including pertinent correspondence with the manufacturer and FDA.

(7) Provide explicit information on who will provide medical care for the subject during the duration of the study.

(8) Indicate the nature and duration of the physician-patient relationship. Define the time at which the patient will no longer be considered part of the study.

(9) Indicate the follow-up procedure to be employed including the manner in which data on side effects, onset and duration of menstruation, and pregnancy will be obtained.

Hazards and Precautions:

Indicate the hazards involved in the proposed study and the precautions which will be taken to minimize their occurrance.

Inconvenience or Discomfort to Subject:

(1) List anticipated side effects of the proposed treatment including their severity and frequency and the manner in which they will be monitored. Indicate what measures will be taken in the event of side effects and the individual responsible for instituting such measures.

(2) Provide a concise description of follow-up procedures and subject management (identify the responsible physician) in the event that treatment is interrupted, incomplete or ineffective (Termination of pregnancy in the event of treatment failure is not supportable under this RFP).

Other Pertinent Clinical Information, including references:

(1) Provide any additional information supporting the safety of the proposed medication.

(2) Provide a copy of the informed consent form to be used.

(3) Provide a copy of the approval of the proposed research by the investigator's insitutional review committee and the constitution of that committee.

EXHIBIT I

OUTLINE FOR SUBJECT RECORD

1. Subject identification (code)
2. Estrogen
    - a. name
    - b. source
    - c. formulation (e.g. 2mg tablets)
    - d. daily dose
    - e. frequency of medication
    - f. duration of medication
    - g. route of administration
    - h. if medication was interrupted for any reason, give particulars
3. Interval between unprotected midcycle (coital) exposure and initiation of medication. Give in hours as nearly as possible.
4. Side effects. Indicate severity, duration and onset relative to initiation of medication.
5. Menstruation. Indicate onset relative to initiation of medication duration and any deviation from the usual bleeding patterns.
6. Result of post treatment pregnancy test.
7. Course of action taken if pregnant.
8. Comments. Provide such other information as may be considered useful including any reported coital exposure between the initiation of medication and the expected onset of menses.

EXHIBIT II

Standard Format for Proposal of Clinical Research Project

Clinical Project Number ________
(To be assigned by the Board)

Date ____________________

To : Chairman, Clinical Research Committee

Recommended by : ____________________, Branch Chief

____________________, Clinical Director

Project Title:

Principal Investigator:

Associate Investigator:

Estimated Duration of Study:

Number of Patients or Volunteers Needed:

Kind of Subjects Needed:	Volunteers	________	Patients	________	
	Age Range	________	to	________	years
	Sex: Male	________	Female	________	
	Other Requirements:				

Narrative description incorporating the following headings:

Purpose of Project:

Project Protocol:

Hazards and Precautions:

Inconvenience or Discomfort to Subject:

Other Pertinent Clinical Information, including references:

Indication of Radiation Committee approval, if appropriate:

General Information

Purpose of the Protocol: The research protocol represents a formal record of the intent of the investigator. This could be important in the rare event of medicolegal action. It must be specific but at the same time should be written to provide a reasonably elastic framework for research, avoiding unnecessary submission of addenda to permit minor changes in the study.

II. Content and Format of Proposals

Forty copies of each proposal are required. No special application forms are provided. Proposals should be typed on 8 x 10 1/2 or 8 1/2 x 11-inch bond paper, preferably single spaced. Pages must be numbered consecutively throughout the proposal. Each copy of a proposal should be bound and/or fastened within a folder. Any unbound material should show the name of the offeror and the principal investigator, and title of the research proposal.

Proposals will be received in Building 31, Room 3A-22, National Institutes of Health, not later than the time specified in the covering letter of this RFP. Telegrams will not be accepted.

One of the forty copies submitted must be signed by an individual authorized to bind the offeror contractually. In addition, the Administrative Certifications and Legal Requirements form accompanying this RFP must be completed, signed and returned.

The proposal should be organized as follows:

1. Cover

The cover of the folder must indicate:

a. that the proposal is submitted in response to the RFP number specified in the covering letter;
b. name and address of offeror;
c. name of the proposed project director (principal investigator);
d. identification of copy bearing institutional signatures;
e. estimated total cost to the Government.

2. Title Page

a. the title of the research project;
b. the name, title, address, and telephone number of:
    (1) the principal investigator;
    (2) the official (e.g., department chairman, dean) authorizing the research proposal;
    (3) the official authorized to bind the offeror contractually.

3. Table of Contents

Indicate page locations for each of the principal sections of the proposal and additional detail as appropriate. A tab index may be helpful for lengthy proposals.

4. Summary and Workscope

Provide a brief summary (not to exceed one page) which states as explicitly as possible the nature and scope of the proposal.

5. Research Proposal

a. Introduction

Describe the overall design of the project and how it is related to the goals of the program as described in this RFP.

b. Specific Aims

Provide a detailed description of the specific studies to be carried out, paying special attention to research to be conducted and results anticipated during the contract period. Describe the study design in detail, and indicate a time schedule for completion of different phases of the proposed project.

c. Methods

Provide a detailed description of the methods to be used, with technical details and a thorough evaluation of the limitations and feasibility of the methods proposed.

d. Previous Work in this Area

Describe previous work in areas relevant to the program objectives described in this Request for Proposals; provide appropriate citations. Indicate what preliminary studies have been carried out and the results of these pilot studies.

6. Qualifications of Scientific Personnel

Provide biographic sketches and pertinent bibliographies for professional personnel that would be involved in the proposed project.

7. Facilities and Equipment

a. It is the policy of HEW that equipment and other facilities required in the performance of Government contracts for research and development will be furnished by the contractor. In exceptional instances, some equipment may be leased or purchased using contract funds, provided the equipment is justified as essential to the successful conduct of the research. In these cases, the offeror must certify that "there is no practicable or economical alternative to providing contract funds for the lease or purchase of the equipment." (Please note - one of the factors to be used in the review and evaluation of each proposal is the adequacy of the facilities and resources available, including the necessary equipment to carry out the proposed project.)

b. The offeror shall describe existing facilities and equipment available for conducting the proposed project and justify in terms of research needs any new facilities or equipment to be acquired and paid for by the contract.

8. Other Research Support

List all active and pending research support (grant or contract) of the major participants, indicating supporting agency; project number, investigator, project title, and level of annual funding.

Where the proposal submitted in response to this RFP is closely related to or overlaps with the research workscope and/or funding of any active or pending support from any source, indicate how the multiple sources of support would be interrelated and/or what support would be relinquished. While more than one source of support may be applied toward a research project (and for some projects this may be advantageous) duplication of funding for specific items is not allowable.

9. Types of Contracts

The proposed price for performance of the work in response to this Request for Proposals shall be in accordance with one of the following contract types:

a. Cost Sharing
b. Cost Reimbursement
c. Cost Reimbursement plus a Fixed Fee

10. Performance Period

Offerors are requested to furnish their own estimates of time required to achieve the objectives of this research. It is anticipated that several contracts will be awarded under this RFP each of which may include a performance period of between one and five years.

11. Incremental Funding:

A. An incrementally funded contract is one in which a total effort or job is described for a multiple year period and under which funds are allotted from time to time to cover increments of performance.

B. It is NIH policy in connection with projects of multiple year duration that resulting contracts will be fully funder whenever possible to cover the entire period of performance.

C. In the event sufficient funds are not available to cover the entire proposed project it is the Governments' intention to negotiate and award some of the contracts with incremental funding features as described in the attached General Provision entitled: "Limitation of Funds." Under this article, which will be included in the contract as awarded, an initial amount will be obligated under the basic contract covering the first year of performance. Additional funds will be allotted from time to time by contract modification up to the full estimated cost set forth in the contract. While it is the Government's intention to progressively fund this project up to the full estimated amount over the entire period of performance, the Government will not be obligated to reimburse the contractor for costs in excess of periodic allotments, nor will the contractor be obligated to continue performance in excess of amounts allotted.

D. The "Limitation of Funds" article to be included in contract as awarded, will supersede the "Limitation of Cost" article in the preprinted General Provisions (HEW-316).

E. Offerors are expected to respond with technical and pricing proposals for the entire period of performance, broken down to reflect time phased increments of work. Contract negotiations will proceed on the basis of work required for phased increments and the entire multiple year project. The resulting contract workscope will describe the total project, but time-phased consistent with planned allotments. The performance period in the basic contract will reflect the total estimated time to complete the entire project.

12. Budget

The proposed estimated costs must be presented according to the following format:

a. Detailed breakdown of the estimated cost for each phase of the contract period. This should integrate the estimated cost of any individual subprojects (paragraph b) and, where feasible, subcontracts, by combining identical items consecutively. Where applicable, detailed estimated costs should be provided for each subproject and subcontract.

b. The detailed estimated costs should be broken down into the following categories:

Project Director (Principal Investigator) and senior personnel (give name, title, and social security number of each)
Other personnel
Supplies (items, quantity, and estimated price per unit)
Equipment (items, quantity, estimated price per unit and total)--purchase or lease
Travel (destination, duration, purpose and cost--per diem and transportation)
Subcontracting(basis, type and detail breakdown of cost)
Consultants (give name and social security number)
Other direct costs (itemize large categories)
Overhead (% of item(s)_______above)
Total estimated cost to the Government

(1) cost incurred within the United States
(2) cost incurred outside the United States (specific breakdown should be provided)

The listing of personnel should indicate the percent of time or effort of all positions (regardless of the source of their salary support) as well as the salary and fringe benefits of each person who would be supported by this contract. Social security numbers must be provided. Justification is required for all principal budget items.

c. Indicate the name and address of the cognizant Government audit agency, if any.

13. Human Subjects

Prospective contractors being considered for award will be required to give acceptable assurance that the project described herein will be subject to initial and continuing review by an appropriate institutional committee. This review shall assure that the rights and welfare of the individuals involved are adequately protected, that the risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent will be obtained by methods that are adequate and appropriate.

The proposal should be appropriately marked in the space provided on the form, or a statement similar to the following, as appropriate, should be entered on the right hand margin of the page bearing the name of the institutional official authorized to sign or execute proposals for the institution:

(a) "Human Subjects--Reviewed and Approved on ___(Date)_______."

NOTE: This date should be no later than 90 days prior to the submission date, and must not be more than 12 months prior to the proposed starting date.

(b) "Human Subjects--Review Pending on _(Date)_____."

NOTE: This date should be at least 1 month earlier than the proposed starting date on the project to avoid possible conflict with the award date.

14. Royalties

Offerors are requested to furnish information in their proposals if any royalties are anticipated to be paid in connection with their performance of work under this contract.

III. Method and Criteria for Review of Proposals

Proposals will be evaluated in accordance with the following factors, listed in order of their relative importance:

1. The scientific merit of the proposed research and its relevance to the program outlined in this Request for Proposals;
2. The clinical experience and technical competence of the personnel participating in the investigation;
3. Prior experience in the use of estrogens as postcoital contraceptive agents;
4. The annual number of subjects expected to participate in the study;
5. The adequacy of the facilities, equipment and medical care available to carry out the proposed project.

A best-buy analysis will be performed, taking into consideration the results of the technical evaluation, price analysis, past performance history, and the ability to complete the work within the required time frame.

Each proposal will be evaluated separately and independently on the basis of the above factors by an ad hoc review panel composed mostly of non-governmental scientists, and by the NICHD Contract Review Committee.

A separate cost analysis and evaluation will be performed by the Contract Specialist.

IV. Administrative Certifications and Legal Requirements

A. Instructions, Terms, Conditions and Provisions

NOTICE OF REQUIREMENT FOR CERTIFICATION OF NONSEGREGATED FACILITIES

Offerors are cautioned as follows: By signing this offer, the offeror will be deemed to have signed and agreed to the provisions of the "Certification of Nonsegregated Facilities" in this solicitation. The certification provides that the offeror does not maintain or provide for his employees facilities which are segregated on a basis of race, creed, color or national origin, whether such facilities are segregated by directive or on a de facto basis. The certification also provides that he will not maintain such segregated facilities. Failure of an offeror to agree to the Certification of Nonsegregated Facilities will render his offer nonresponsive to the terms of solicitations involving awards of contracts exceeding $10,000 which are not exempt from the provisions of the Equal Opportunity clause.

NOTE: Offers must set forth full, accurate and complete information as required by the solicitation (including attachments). The penalty for making false statements in offers is prescribed in 18 U.S.C. 1001.

1. GENERAL INSTRUCTIONS

(a) The offeror is requested to promptly acknowledge receipt of the Request for Proposals (RFP) and advise the issuing office whether he intends to submit a proposal.

(b) Hand delivered proposals must be received at the place designated for receipt of proposals prior to the specific time set forth in the RFP letter.

2. PREPARATION OF OFFERS

(a) Offerors are expected to examine all Sections of this Request for Proposals and to comply with the instructions, terms and conditions set forth herein. Failure to do so will be at the offeror's risk.

(b) Offeror shall furnish the information required by this solicitation. The proposal must be signed by an official authorized to bind the offeror. Offers signed by an agent are to be accompanied by evidence of his authority unless such evidence has been previously furnished to the issuing office.

(c) Offeror must state a definite time for performance of the research (Period of Performance).

3. SUBMISSION OF OFFERS

Offers and modifications thereof shall be addressed to the office designated for the receipt of offers (as specified in the covering letter attached to this solicitation). The offeror shall show the Request for Proposals number and the name and address of the offeror on the face of the envelope.

The Government will require a minimum of one hundred-twenty (120) days for review and acceptance or rejection of proposals.

If not offer is to be submitted, do not return the solicitation. If you do not wish to receive future solications, please submit a postcard or letter to that effect.

This solicitation does not commit the Government to pay for any costs incurred in the preparation or submission of proposals, nor to contract for any research and development services described herein.

4. LATE PROPOSALS

The Government has established a schedule for award of a contract. Late proposals will be not be considered unless they offer substantial benefit to the Government which would warrant consideration in conjunction with timely offers received.

5. WITHDRAWALS

The Government reserves the right to consider proposals or modifications thereof received after the date indicated for such purpose, but before award is made, should such action in the interest of the Government. Offers may be withdrawn by written or telegraphic notice received at any time prior to award. Offers may be withdrawn in person by an offeror or his authorized representative, provided his identity is made known and he signs a receipt for the offer prior to award.

6. AWARD OF CONTRACT

(a) A contract may be awarded to the responsive and responsible offeror whose offer conforming to the solicitation will be most advantageous to the Government, price and other factors considered. The Government reserves the right to accept other than the lowest price proposal.

21.

(b) The Government reserves the right to reject any or all offers and to waive informalities and minor irregularities in offers received.

(c) The Government reserves the right to make an award without further discussion of the proposals submitted. Therefore, the proposal should be submitted initially on the most favorable terms from both price and technical standpoint which the offeror can propose to the Government. The offeror shall specifically stipulate that the proposal is predicated upon the acceptance of all the terms and conditions contained in the Request for Proposals. It is understood that the proposal will become a part of the official file on this matter without obligation to the Government.

7. AWARD INFORMATION

After the closing date for receipt of proposals, no source selection information will be furnished until after award has been made.

8. UNNECESSARILY ELABORATE PROPOSALS

Unnecessarily elaborate brochures or other presentations beyond that sufficient to present a complete and effective proposal are not desired and may be construed as an indication of the offeror's lack of cost consciousness. Elaborate art work, expensive paper and bindings and expensive visual and other presentation aids are neither necessary nor wanted.

9. CONFIDENTIALITY OF PROPOSALS

(a) Every effort will be made to treat your proposal in confidence. Ordinarily, proposals will not be disclosed to any person not directly involved in the evaluation process.

(b) However, in the event your proposal contains data which you may not want disclosed to the public or used by the Government for any purpose other than evaluation of proposals, the front page of your proposal should include the legend set forth below:

> Technical data contained in pages ______ of this proposal shall not be used or disclosed, except for evaluation purposes, provided that if a contract is awarded to this submitter as a result of or in connection with the submission of this proposal, the Government shall have the right to use or disclose this technical data to the extent provided in the contract. This restriction does not limit the Government's right to use or disclose any technical data obtained from another source without restriction.

10. ATTACHMENT A

The contract format and General Provisions (HEW 315-rev. 8/64) as shown in Attachment A will be used for educational institutions.

11. ATTACHMENT B (Not attached if Educational Institution)

The contract format and General Provisions (HEW 316-rev. 3/72) as shown in Attachment B will be used for cost-plus-fixed-fee contracts. Minor modifications will be made to the format for cost reimbursement contracts without fee with commercial and non-profit organizations.

IV. Administrative Certifications and Legal Requirements

B. Representations and Certifications

THIS ATTACHMENT (PAGE 23 THROUGH 29) SHALL BE EXECUTED
BY AN OFFICIAL AUTHORIZED TO BIND THE OFFEROR,
DETACHED AND RETURNED WITH THE SIGNED COPIES OF THE PROPOSAL

RFP NO.____________________

CLOSING DATE FOR THIS RFP IS____________________

NAME OF OFFEROR______________________________

PRINCIPAL INVESTIGATOR'S NAME____________________

The offeror makes the following representations and certifications as part of his proposal (check or complete all appropriate boxes or blanks):

1. SMALL BUSINESS REPRESENTATION

   That he __IS, __IS NOT, a small business concern. (A small business concern for the purpose of Government procurement is a concern, including its affiliates, which is independently owned and operated, is not dominant in the field of operations in which it is submitting offers on Government contracts, and can further qualify under the criteria prescribed by the Small Business Administration as set forth in Title 13, Part 121, of the Code of Federal Regulations.)

2. TYPE OF ORGANIZATION

   That he operates as an ___individual, __partnership, ___joint venture, __corporation, incorporated under the laws of the state of ____________________, __nonprofit, __public, __private, __educational institution or affiliate.

3. CONTINGENT FEE REPRESENTATION (FPR 1-1.505)

   That (a) he __HAS, __HAS NOT, employed or retained any company or person (other than a full-time, bona fide employee working solely for the contractor) to solicit or secure this contract, and (b) he __HAS, __HAS NOT, paid or agreed to pay any company or person (other than a full-time bona fide employee working solely for the contractor) any fee, commission, percentage, or brokerage fee contingent upon or resulting from the award of this contract; and agrees to furnish information relating to (a) and (b) above as requested by the Contracting Officer. (For interpretation of the representation, including the term "bona fide employee" see Code of Federal Regulations, Title 41, Chapter I, Subpart 1-1.5.)

If the offeror, by checking the appropriate box provided therefor, has represented that he has employed or retained a company or person (other than a full-time bona fide employee working solely for the offeror) to solicit or secure this contract, or that he has paid or agreed to pay any fee, commission, percentage, or brokerage fee to any company or person contingent upon or resulting from the award of this contract, he shall furnish, in duplicate, a complete Standard Form 119, Contractor's Statement of Contingent or Other Fees. If offeror has previously furnished a completed Standard Form 119 to the office issuing this solicitation, he may accompany his offer with a signed statement (a) indicating when such completed form was previously furnished, (b) identifying by number the previous solicitation or contract, if any, in connection with which such form was submitted, and (c) representing that the statement in such form is applicable to this offer.

4. EQUAL OPPORTUNITY REPRESENTATION (FPR 1-12.805-4)

That he __HAS, __HAS NOT, participated in a previous contract or subcontract subject either to the Equal Opportunity clause herein or the clause originally contained in Section 301 of Executive Order 10925, or the clause contained in Section 201 of Executive Order 11114; that he __HAS, __HAS NOT, filed all required compliance reports; and that representations indicating submission of required compliance reports, signed by proposed subcontractors, will be obtained prior to subcontract awards. (The above representation need not be submitted in connection with contracts or subcontracts which are exempt from the clause.)

5. AFFIRMATIVE ACTION PROGRAM REPRESENTATION (FPR 1-12.805-4)

That (a) he __HAS developed and has on file, __HAS NOT developed and does not have a file at each establishment affirmative action programs as required by the rules and regulations of the Secretary of Labor (41 CFR 60-1 and 60-2), or (b) he __HAS NOT previously had contracts subject to the written affirmative action program requirement of the rules and regulations of the Secretary of Labor.

Note: If the answer to (a) above is negative, complete the following:

__ Offeror is an agency or instrumentality of state or local government.

__ Offeror employees fewer than 50 persons.

__ Offeror has not been awarded a Federal contract or subcontract of $50,000 or more since July 1, 1968.

6. CERTIFICATION OF NONSEGREGATED FACILITIES (FPR 1-12.803-10(d)(1))

(Applicable to (1) contracts, (2) subcontracts, and (3) agreements with applicants who are themselves performing federally assisted construction contracts, exceeding $10,000 which are not exempt from the provisions of the Equal Opportunity clause.)

By the submission of this offer, the offeror, applicant, or subcontractor certifies that he does not maintain or provide for his employees any segregated facilities at any of his establishments, and that he does not permit his employees to perform their services at any location, under his control, where segregated facilities are maintained. He certifies further that he will not maintain or provide for his employees any segregated facilities at any of his establishments, and that he will not permit his employees to perform their services at any location, under his control, where segregated facilities are maintained. The offeror, applicant, or subcontractor agrees that a breach of this certification is a violation of the Equal Opportunity clause in this contract. As used in this certification, the term "segregated facilities" means any waiting rooms, work areas, rest rooms and wash rooms, restaurants and other eating areas, time clocks, locker rooms and other storage or dressing areas, parking lots, drinking fountains, recreation or entertainment areas, transportation, and housing facilities provided for employees which are segregated by explicit directive or are in fact segregated on the basis of race, color, religion, or national origin, because of habit, local custom, or otherwise. He further agrees that (except where he has obtained identical certifications from proposed subcontractors for specific time periods) he will obtain identical certifications from proposed subcontractors prior to the award of subcontracts exceeding $10,000 which are not exempt from the provisions of the Equal Opportunity clause; that he will retain such certifications in his files; and that he will forward the following notice to such proposed subcontractors (except where the proposed subcontractors have submitted identical certifications for specific time periods):

NOTICE TO PROSPECTIVE SUBCONTRACTORS OF REQUIREMENT FOR CERTIFICATIONS OF NONSEGREGATED FACILITIES

A Certification of Nonsegregated Facilities must be submitted prior to the award of a subcontract exceeding $10,000 which is not exempt from the provisions of the Equal Opportunity clause. The certification may be submitted either for each subcontract or for all subcontracts during a period (i.e., quarterly, semi-annually, or annually).

7. CERTIFICATION OF INDEPENDENT PRICE DETERMINATION (FPR 1-1.317)

(a) By submission of this offer, the offeror certifies, and in the case of a joint offer, each party thereto certifies as to its own organization that in connection with this procurement:

(1) the prices in this offer have been arrived at independently, without consultation, communication, or agreement, for the purpose of restricting competition, as to any matter relating to such prices with any other offeror or with any competitor;

(2) unless otherwise required by law, the prices which have been quoted in this offer have not been knowingly disclosed by the offeror and will not knowingly be disclosed by the offeror prior to opening in the case of an advertised procurement or prior to award in the case of a negotiated procurement, directly or indirectly to any other offeror or to any competitor; and

(3) no attempt has been made or will be made by the offeror to induce any other person or firm to submit or not to submit an offer for the purpose of restricting competition.

(b) Each person signing this offer certifies that:

(1) he is the person in the offeror's organization responsible within that organization for the decision as to the prices being offered herein and that he has not participated and will not participate in any action contrary to (a)(1) through (a)(3) above; or

(2) (i) he is not the person in the offeror's organization responsible within that organization for the decision as to the prices being offered herein but that he has been authorized in writing to act as agent for the persons responsible for such decision in certifying that such persons have not participated, and will not participate in any action contrary to (a)(1) through (a)(3) above, and as their agent does hereby so certify; and (ii) he has not participated and will not participate, in any action contrary to (a)(1) through (a)(3) above.

10. PERIOD OF ACCEPTANCE

That it will allow ______ days from the date of this proposal for acceptance thereof by the Government (a minimum of 120 days should be allowed).

11. DUPLICATION OF COST

The offeror represents, by submission of this offer, that any charges contemplated and included in its estimate of cost for performance are not duplicative of any charges against any other Government contract, subcontract, or other Government source.

12. ADDITIONAL CERTIFICATIONS

The Certificate of Current Cost or Pricing Data is applicable to all contracts expected to exceed $100,000, with the exception of contracts for basic research with educational institutions. Attachment I entitled "Certificate of Current Cost or Pricing Data" should be retained by the offeror and executed after contract negotiations have been completed and prior to award of the contract.

NOTE: The penalty for making false statements in offers is prescribed in 18 U.S.C. 1001.

Submitted on Behalf of: ______________________________ Date ______________

By ______________________________
Signature of Authorized Individual

____
Typed Name and Title

ATTACHMENT I

CERTIFICATE OF CURRENT COST OR PRICING DATA

This is to certify that, to the best of my knowledge and belief, cost or pricing data[1] submitted in writing, or specifically identified in writing if actual submission of the data is impracticable (see § 1-3.807-3(h)(2)), to the Contracting Officer or his representative in support of ______________________________[2] are accurate, complete, and current as of ______________________________.[3]
(Date)

____
NAME OF FIRM

____
SIGNATURE OF OFFICIAL

____
DATE OF EXECUTION[4]

____
TYPED NAME AND TITLE OF OFFICIAL

---

[1] For definition of "cost or pricing data," see FPR § 1-3.807-3.

[2] Describe the proposal, quotation, request for price adjustments, or other submission involved, giving appropriate identifying number (e.g., RFP No. ______).

[3] This date shall be the date when the price negotiations were concluded and the contract price was agreed to. The responsibility of the contractor is not limited by the personal knowledge of the contractor's negotiator if the contractor had information reasonably available (see § 1-3.807-5(a)) at the time of agreement, showing that the negotiated price is not based on accurate, complete, and current data.

[4] This date should be as close as practicable to the date when the price negotiations were concluded and the contract price was agreed upon.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

December 19, 1972

PROGRESS REPORT

ON

DIETHYLSTILBESTROL (DES) IMPLANTS IN CATTLE

Commissioner Edwards has asked me to keep you advised on the progress of studies being conducted by the U. S. Department of Agriculture (USDA) on the use of DES implants in cattle.

The Food and Drug Administration (FDA) has prepared a progress report on this study. A copy of it and supporting data from USDA is attached.

If you have any questions on this matter or wish additional copies of the attached material, please call me or a member of my staff. Our telephone number is: 443-3793.

Sincerely yours,

Gerald F. Meyer

Gerald F. Meyer, Director
Office of Legislative Services

Attachment

December 18, 1972

Food and Drug Administration
Progress Report
on
The Status of DES as an Animal Growth Promotant

Diethylstilbestrol (DES) has been used for over 20 years as a growth promotant in animals, administered both through feed and by implants. Its use results in a more rapid weight gain by cattle, thus reducing the cost of meat. When use of DES was questioned in the early 1960's because of its known carcinogenicity, Congress passed a special amendment to the Federal Food, Drug, and Cosmetic Act, explicitly requiring the Food and Drug Administration to approve this use as long as no residue is found in the meat using available analytical methodology and under conditions of use that are reasonably certain to be followed in practice.

I. DES in Animal Feed.

During mid-1972, the United States Department of Agriculture conducted new studies to determine whether detectable residues occurred in the edible portion of animals fed DES. These studies used radioactive tracers, the most sensitive research tool available today. USDA reported no detectable residues in animal muscle tissue, which represents the vast bulk of the country's meat supply. Detectable residues were found in animal liver at a level of .21 and .52 parts per billion (ppb), however, after withdrawal for seven days. FDA therefore withdrew approval of DES in animal feed in an order published in the Federal Register on August 4, 1972. The order denied a public hearing on the matter, prohibited any further manufacture of such products, and permitted continued use of already-manufactured DES premixes and feed until January 1, 1973.

The validity of the August 4, 1972 Federal Register order has been challenged in the courts by three manufacturers of DES. A request for a stay of the order pending the court appeal was denied both by FDA and by the United States Court of Appeals for the District of Columbia Circuit.

Recent USDA studies using the same radioactive tracer techniques show no DES residues in animals withdrawn from DES feed for 10 or 14 days. FDA has ruled that this is insufficient, by itself, to reinstate approval of DES for use in animal feed.

Several Senators and Congressmen have requested FDA to withdraw its August 4 order and to conduct a public hearing on the matter. FDA has denied these requests. A number of Senators and Congressmen have also requested FDA to withdraw its phase-out of DES in animal feed, and FDA has also denied these requests.

The time for use of DES in animal feed expires on January 1, 1973. FDA has asked USDA to emphasize to all farmers that any use of DES in animal feed after that date represents a criminal offense. FDA is requesting premix manufacturers to recall any product that has not been mixed with feed and will monitor this recall. Feed mills and feeders who have recently received significant shipments of the banned product will be inspected. Prompt regulatory action will be taken against any detected illegal activity.

II. DES in Implants.

The USDA study on which the August 4, 1972 FDA order was based did not include use of DES in implants. Earlier testing had shown a similar potential for residues from implants. Based upon FDA field investigations no residues had been found by USDA's regular monitoring in animals administered DES solely by implant, and there was no evidence on which to base an order withdrawing approval of DES implants.

FDA concluded at that time that no public health hazard existed as a result of continued use of DES in implants pending further tests. Recent data confirm that conclusion.

FDA therefore announced in its August 4 order that it was premature to rule at that time on the use of DES in implants. A ruling on this matter was held in abeyance pending the results of separate testing on implants just begun by USDA, the results of which were to be available within several weeks.

On December 13, 1972, USDA transmitted to FDA, at FDA's request, the available data from the ongoing USDA radioactive tracer study on implants. A copy of that transmittal is attached.

The USDA progress report on this study contains partial information on one steer implanted with 30 mg. DES and killed 30 days after implanting, one steer implanted with 30 mg. DES and killed 60 days after implanting, and one untreated steer killed as a control. No radioactivity was found in any muscle tissue of any of the animals.

This was similar to the earlier finding of no DES residue in muscle tissue of animals fed DES in animal feed. Radioactivity, indicating possible DES residues, was found at a level of .42-.55 parts per billion (ppb) in both the kidney and the liver of the 30-day and 60-day steers. Originally one laboratory reported 0.7 ppb in the kidney of one steer using the gas-liquid-chromatography (see paragraph 2 of the progress report). Subsequent retests by two laboratories led to the conclusion that this tissue was negative.

The USDA progress report states that "the identity of the radioactivity in the liver and the kidney is not known." Further analytical work is needed to verify that this radioactivity in whole or in part represents DES specifically. This work has thus far not been successful because of the difficulty of analysis at these low levels. This confirmatory procedure may be appropriate for implants, whereas it was not necessary for the study using DES in animal feed, because autodegradation of DES occurs over the period of time that implants remain in the steer and thus raises the possibility that some of the radioactivity detected in the study may be a false positive. In spite of the uncertainty whether all or only a part of the radioactivity detected in the study is due to DES, FDA scientists have concluded that there is no question but that at least some of this activity is caused by DES.

There are presently seven new animal drug applications (NADA's) approved by FDA for use of DES in implants for growth promotion in cattle and sheep. All but two of these NADA's state in the labeling that the animal is not to be slaughtered for 120 days after implantation. A finding of some DES residue at 30 and 60 days is insufficient to withdraw approval of DES marketed under labeling which calls for slaughter no sooner than 120 days after implanting.

Additional USDA studies now in progress will provide information on whether DES residues are found at up to 120 days after implantation. Two additional animals are scheduled to be slaughtered, one after 60 days and the other after 120 days, within the next two weeks as a part of the USDA study. Additional animals will be slaughtered at the 120-day period in another few weeks. The entire USDA study is scheduled to be completed about March 15, 1973. FDA will review these results as they become available to determine whether they constitute adequate scientific data to justify withdrawing approval of DES in implants under existing labeling which provides for a minimum of 120 days before slaughter.

If any residue of DES is found in liver or kidneys 120 days after implant, all approval of DES for this use will immediately be withdrawn. In that event, any further use of DES implants would become unlawful effective as of the date of publication of the notice in the Federal Register.

In the interim, the Food and Drug Administration is taking the following immediate steps pending receipt of further results from the ongoing USDA study.

1. FDA has wired the holders of the two NADA's whose labeling provides for a period less than 120 days (21 and 70 days respectively) between implantation and slaughter, to require that use of this labeling cease immediately. Labeling on any DES implants shipped by these two companies in the future must contain a 120-day minimum period between implantation and slaughter.

2. FDA has requested USDA to require certification from producers that implantation occurred at least 120 days prior to slaughter. This will be monitored as part of the existing USDA certification program involving DES.

3. USDA will continue to monitor meat for DES residues. Thus far, there has been no instance in which a DES residue was found by USDA in an animal receiving DES solely by implant. Since DES can be administered only by implant after January 1, very close monitoring of this use will be possible.

4. FDA is requesting the industry to expedite development of a type of implant that can be completely absorbed in a specified period of time, or that otherwise meters out DES in a uniform way that can closely control the time of administration of DES. Any such development or label changes which increases the safety of DES in this use will be adopted as a requirement, if the use of DES is not totally withdrawn as a result of data provided by the current USDA studies.

5. FDA is informing the animal feeders and the drug industry that if the USDA study shows no detectable residue after 120 days, FDA will require additional controls (e.g., a method of identifying each animal with the date of implant) to make certain that this period is observed.

FDA has been in regular contact with Canadian officials responsible for use of DES as a growth promotant in that country. Canada will discontinue the sale of DES in any form after January 1, 1973. Since all use of DES in feed in the United States must cease as of January 1, and a decision will be made with respect to DES implants as soon as the pertinent results of the USDA study are available, the action on DES in this country is within the time schedule being applied in Canada.

Attachment

DEPARTMENT OF AGRICULTURE
OFFICE OF THE SECRETARY
WASHINGTON, D. C. 20250

December 13, 1972

Dr. Charles C. Edwards
Commissioner of Food and Drugs
Food and Drug Administration
4600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Edwards:

Enclosed is the information which your office requested as a result of my telephone conversation with Dr. Sherwin Gardner on Monday.

You will note in the last paragraph of Dr. Rumsey's letter of October 6, 1972, that the data are preliminary in nature and that probably final conclusions should not be drawn until the remaining data from the experiment has been obtained and analyzed. You will also note that one GLC measurement from one laboratory on one kidney sample was 0.7 ppb. This was analyzed again at Beltsville and was found negative. The GLC analyses conducted independently by APHIS were negative on all four samples. The meaning of the radio-carbon values on these four samples has not been determined as to their association with DES molecules.

Sincerely,

N. P. Ralston

N. P. RALSTON
Associate Director
Science and Education

Enclosure

UNITED STATES DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH SERVICE
Nutrition Institute, Ruminant Nutrition Laboratory
Beltsville, Maryland 20705

October 13, 1972

Subject: Progress Report of DES Research at Beltsville

To: T. W. Edminster
Administrator, ARS

I. ^{14}C-Labeled DES Implant Study. Additional labeled implants were received from Hess and Clark 10/12/72. Steers will be treated starting 10/16/72.

II. ^{14}C-Labeled DES Oral Study. One steer and one heifer have been slaughtered following 14 days withdrawal of oral DES. The analysis of tissues is not complete; however, radiocarbon could not be detected in urine and feces after 11 days.

T. S. Rumsey
Research Animal Scientist
Ruminant Nutrition Laboratory

cc:
S. C. King
P. D. DeLay
A. A. Hanson
W. Hertz
R. R. Oltjen
E. J. Warwick

UNITED STATES DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH SERVICE
Nutrition Institute, Ruminant Nutrition Laboratory
Beltsville, Maryland 20705

not sent until 10/16 to Dr. Van Houweling

October 6, 1972

Subject: Progress Report of DES Research at Beltsville

To: T. W. Edminster
Administrator, ARS

^{14}C-Labeled DES Implant Study. Two steers have been slaughtered following implantation with ^{14}C-labeled DES according to the schedule outlined in our earlier correspondence. The steers were fed a conventional finishing ration. Steer No. 445 was implanted with 29.5 mg of labeled DES (2 implants) and killed 60 days after implanting and steer No. 312 was implanted with 30.2 mg (2 implants) and killed 30 days after implanting. An untreated steer was treated similarly and killed as a control. The attached table contains the radiocarbon content of tissues and the results of gas chromatography analyses for CIS and TRANS DES which were conducted by independent laboratories.

On the basis of the two gas-liquid-chromatography analysis of the tissue, the two implanted steers did not appear to contain a significant amount of DES above 0.5 ppb in the liver. The kidney from steer 312 (30 day) was found to have 0.7 ppb DES by the Ruminant Nutrition Laboratory and negative results by the APHIS Laboratory. Time has not permitted us to analyze muscle tissues by GLC. These will be conducted in the near future.

The radiocarbon analysis indicates a level of activity equivalent to 0.42 to 0.51 ppb in the liver and 0.53 to 0.55 in the kidney of the 60 and 30 day steers, respectively. Activity above background was not detected in muscle tissues. The identity of the radioactivity in the liver and kidney is not known. An analysis by a mass spectrometer would be needed to verify the identity of the compound(s). It is questionable that at these low levels a mass spectrometer analysis will actually define what the radiocarbon is associated with. We are, however, exploring the possibilities of concentrating the samples to determine the structural identity of the residue(s) by mass spectrometer. The recovered implants have not been examined for autodegradation. Autodegradation would result in the "ppb equivalents" as expressed in the table being overestimates.

We are proceeding with the analysis of the remaining tissue, urine, feces, and blood samples and also the analysis of the retrieved implants.

We have not received the additional labeled implants and, therefore, do not have a time schedule for treating additional steers. Dr. Ray of Hess and Clark indicated this morning that the implants will be shipped October 10, 1972. We will be able to implant three steers within four days after the implants arrive.

We are enclosing for your information the experimental outlines for both our "hot" and cold implant studies. We feel that the results in this memo are preliminary in nature and that possibly final conclusions should not be drawn until the data from the remaining 10 steers in the "hot" implant and data from the cold implant studies are in.

Theron S. Rumsey

T. S. Rumsey
Research Animal Scientist
Ruminant Nutrition Laboratory

1 Attachment
Enclosures

cc:
S. C. King
P. D. DeLay
E. J. Warwick
A. A. Hanson
W. Mertz

TISSUE ANALYSIS OF STEERS IMPLANTED WITH ^{14}C-DES

Tissue	Animal No.	Days after implantation	Radiocarbon analysis (Lab 1) b/		Gas chromatography analysis	
			dpm per gram dry tissue above control a/	ppb equivalent wet tissue	Laboratory 1	Laborato 2
Liver	312	30	884.4	0.51	Neg. c/	Neg.
	445	60	726.5	0.42	Neg.	Neg.
Kidney	312	30	1227.5	0.55	0.7	Neg.
	445	60	917.5	0.53	Neg.	Neg.
Rib eye Muscle	312	30	N.S. d/	--		
	445	60	N.S.	--		
Shoulder Muscle	312	30	N.S.	--		
	445	60	N.S.	--		

a/ Sample counts of 87.5 net dpm per gram of dry tissue are necessary for significance above background at the .01 level of probability and 58.7 net dpm at the .05 level of probability.

b/ Laboratory 1, Ruminant Nutrition Laboratory; Laboratory 2, APHIS.

c/ Samples are reported negative when below 0.5 ppb which is the level of quantitation.

d/ Non-significant above background at .05 level of probability.

U.S. SENATE,
Washington, D.C., March 5, 1973.

Hon. EDWARD M. KENNEDY,
U.S. Senate,
Washington, D.C.

DEAR TED: You know of my interest in the subject of human experimentation. Unfortunately, my schedule prevents me from testifying at the hearing your Subcommittee on Health will be holding over the next few days.

As you may recall, I introduced legislation last year calling for the establishment of a National Human Experimentation Board to set guidelines for human experimentation. On February 21, I introduced a similar bill with the hope that some action will be forthcoming on it this year. I would appreciate it greatly if you would include my floor statement and the text of the bill in the records of the Health Subcommittee's hearing.

Sincerely,

HUBERT H. HUMPHREY.

[From the Congressional Record, Feb. 21, 1973]

STATEMENTS ON INTRODUCED BILLS AND JOINT RESOLUTIONS

By Mr. HUMPHREY: S. 934. A bill to establish within the executive branch an independent board to establish guidelines for experiments involving human beings. Referred to the Committee on Government Operations.

NATIONAL HUMAN EXPERIMENTATION STANDARDS BOARD ACT

Mr. HUMPHREY. Mr. President, I wish to commend the distinguished Senator from Massachusetts (Mr. KENNEDY) and the Subcommittee on Health which he chairs for the hearings they will be conducting this week concerning human experimentation. The field of human experimentation is one in which the public is poorly informed. Yet this area involves the lives of thousands of human subjects and important medical research. Although the hearings will not devote themselves to particular legislation, they will help to provide the Congress with facts we badly need to know.

Mr. President, I am today introducing legislation to protect the rights and indeed the lives of the subjects of human experimentation. I introduced similar legislation last year. Such legislation is needed now more than ever.

The National Human Experimentation Standards Board Act would establish within the executive branch an independent board to set guidelines for experiments involving human beings.

The bill I am introducing today should in no way be interpreted as an attack on the invaluable research done or authorized by the Federal agencies capable of conducting clinical investigation using human subjects. As a result of these efforts, countless thousands of lives have been saved. However, I am concerned that we protect the rights of the human subjects of these investigations.

SHOCKING REVELATIONS

Last year the country was shocked by the revelation in the press of a barbaric syphilis study involving black men which had been conducted over a period of four decades. In Tuskegee, Ala., more than 430 men suffering from syphilis were denied treatment so Public Health Service doctors could study the damage the untreated disease did to human bodies. It was reported that at least 28, and perhaps as many as 107, of the men died from untreated syphilis.

The fact that these men volunteered for the experiment with the promise that they would receive $50 plus burial expenses demonstrates beyond any doubt that consent is a totally inadequate standard for human experimentation.

Subjects for the most dangerous experiments are almost always the poor and the uneducated. They desperately need money and do not fully comprehend the danger to which they will be exposed.

The famous medical authority Henry Knowles Beecher of Harvard University has written that:

"Lay subjects, sick or well, are not likely to understand the full implications of complicated procedures, even after careful explanation."

In some cases individuals unwittingly become test subjects, occasionally with disasterous results. Recently, associates of Ralph Nader have charged the University of Michigan with "the reckless practice of medicine" in dispensing the medication—DES—to coeds who think they may be pregnant after contraceptive failure or unprotected intercourse. DES or diethystilbestrol is a synthetic estrogen which has been linked to cancer when used for purposes other than the prevention of miscarriage in women of child-bearing age.

Another experiment with DES conducted in the early 1950's on 840 women serves as a further example. These women were given the hormone diethystilbestrol and now their daughters, aged 15 to 21, are now found to have an alarmingly high rate of malignancies. One girl has died. One of the participants in the experiment in 1950 was never advised she had been part of the experiment until August 1972.

Ironically much of this experimentation has been fueled by the requirements of recent legislation. The thalidomide scandals of the early 1960's led to the passage of the Harris-Kefauver Act of 1962. This law requires pharmaceutical companies to conduct three stages of human trilas before the Food and Drug Administration allows a drug to be marketed. The sponsor of a drug investigation must obtain signed statements of informed consent from each prospective participant in the experiment, but if a subject is unable to sign, the decision regarding their participation in the investigation can be left to the professional judgment of the investigator.

Federal Drug Administration records show that more than 3,000 drugs are currently being tested. In 1 year alone, 1971, human beings were the subjects of the initial, stage one, tests of more than 500 of these drugs.

The broad range of Federal programs dealing with human experimentation—from population control to cancer—make it imperative that we establish some standards to prevent the creation of human guinea pigs. Professional estimates indicate that 85 to 90 percent of all clinical investigations are Government sponsored and funded. Indeed, Government personnel, like military reserve units, and Government agencies, such as the U.S. Employment Service, are frequent sources of both subjects and information leading to subjects.

It is difficult to determine how many agencies or projects there might be since, in some instances, medical investigations are not clearly stated as involving human subjects.

The principal Federal agences concerned are the Veterans' Administration, the Department of Defense—the Army, Air Force, and Marine Corps—and the National Institutes of Health. The Atomic Energy Commission can become involved in licensing the use of radioisotopes for experimental purposes.

Laws which make each agency ultimately responsible for the nature of its own experiments are inadequate.

NATIONAL GUIDELINES

The Congress should act now to set up national guidelines for human experimentation. There is every indication that clinical investigations will be enormously proliferated in years to come, as cancer research and other major investigative efforts are stepped up.

Mr. President, the Congress would make a serious error in adopting measures which establish informed, voluntary consent as the primary standard governing human experimentation. We have all personally experienced situations in which we were either subtly or overtly coerced into volunteering for something. For example, can anyone honestly believe that there is a total absence of pressures, including psychological pressures, in cases involving prisoners serving extended sentences who volunteer for medical projects in the belief that they might get "good time" before the parole board?

Parole boards are under no obligation whatsoever to commit themselves to reducing the sentences of those who volunteer in our prisons, indeed, established policy is to the contrary. However, we are all aware of cases such as the Leopold case, where parole has occurred accompanied by public statements indicating that the parole resulted from an exceptional voluntary contribution to the advance of medical science. However, most prisoners are not as well educated and as able to assess the risks as Mr. Leopold.

Some prison testing programs have been linked to prison drug traffic, forced homosexual encounters, injuries to inmates, and highly questionable test results. A 1968 Government study of the Holmesburg Prison in Philadelphia revealed that inmate workers for the University of Pennsylvania Medical School testing project often stole and sold drugs used on various experiments. The money paid to inmates participating in the program—more than a quarter of a million dollars each year—provided a great source of patronage to the inmate who controlled the selection of test participants. The study reports that a fraud artist who held such a position used his power to induce men to serve as his homosexual companions for fees of about $1,600 a year.

Prisoners make up almost the entire phase I stage of drug testing programs because they involve risks and pain that would not be sanctioned for student subjects. But reports indicate that behind prison walls the guidelines for human experimentation established by HEW and other agencies are easily disregarded. A recent newspaper article reports that the worst abuses of prisoners take place in exactly those prisons where psychiatrists have the most influence, such as the California Medical Center at Vacaville and the Patuxent Institution in Maryland. This happens because customary constitutional safeguards, at best flimsy in a prison, are completely shattered under the guise of "treating the patient" rather than "punishing the prisoner." The article further states that electroshock, psychosurgery, and massive drug dosing are permitted as treatments when they would be clearly "cruel and unusual" if evaluated as punishments.

While poorly informed prisoners sign up for testing programs for the money or to get away from the boredom of prison life or are unknowingly subjected to unusual medical treatments; persons outside prison walls who are critically ill are often subjected to experimentation without their consent. The same is too often true also in the cases of children, the mentally retarded, and the institutionalized.

In 1967, the late Senator Robert Kennedy discovered one reason why children at Willowbrook State School in Staten Island, N.Y., were willing participants in hepatitis experiments. Parents had been told that the school was too crowded and that their child could not get in—unless the parents would agree to let the youngster join the school's hepatitis testing program.

In a number of municipal hospitals, physicians have succumbed to financial pressures and permitted entire units of the hospitals to be devoted to evaluating new drugs. These units are maintained and staffed by drug companies. Because treatment at public hospitals and prisons is often substandard, physicians may justifiably believe that the medical benefits of testing outweigh the risks.

It appears that many of these physicians have forgotten the admonition of Hippocrates:

"Life is short, and the art long; the occasion instant, decision difficult, experiment perilous."

Despite the American Medical Association's strict codes of research ethics, a recent study found that most physicians engaged in clinical research never studied the ethics of testing while in medical school, and that a "significant minority" place personal and scentific achievement ahead of their responsibility to the test population.

Mr. President, would these physicians care more about the test population if it was composed of U.S. Congressman? Would they be more caring if the human subject were their next-door neighbor? I submit that they would.

It is our moral responsibility to see that the poor, the uneducated, and the captive populations are not left unprotected as human guinea pigs. Prisoners must not be allowed to sel their bodies for $1 a day, not knowing the full consequences of their action. We cannot permit other persons to volunteer the mentally retarded for experiments that are not fully explained and observed. These individuals are asked to bear the burden of medical advancement for all of us. We owe them just protection.

Mr. President, I hasten to assure Members of Congress and the public that I would not hamper the legitimate research in our Nation which has saved so many lives and brought so many of us from sickness to health. Certainly, the overwhelming majority of research is conducted with the strict observance of both medical and ethical considerations. But we must act very carefully to protect our country from abuses we know exist in experiments on human beings, however rare such abuses might, in fact, be. Clearly, many test subjects are incapable of protecting themselves and have no political power to force the passage of adequate safeguards.

In 1946, the American Medical Association passed a resolution on human research. Since then there have been a number of "guiding principles" and "codes of ethics" developed by the medical profession. These promulgations were followed by FDA regulations in 1962 and the Helsinki Declaration of 1966.

All of these guides and codes are pretty much the same. They state that the "informed consent" of the subject must be obtained and that human experiments must be based on prior laboratory work and research on animals. They emphasize the grave responsibility of the investigator to the subject, and exhort him to avoid experiments that are of no scientific value or that subject humans to unnecessary pain and risk.

The principles of previous codes were incorporated in a 1972 U.S. Department of Health, Education, and Welfare publication entitled "The Institutional Guide to DHEW Policy on Protection of Human Subjects." However, despite the concern the guide expresses for captive populations; HEW does not even maintain a list of prisons in which HEW-financed research programs are in progress and has "no central source of information" on the scope of medical experiments on prisoners by drug companies according to a current Atlantic magazine article. The legislation I am introducing today would attempt to solve this information problem as well as establish national human experimentation guidelines.

THE NATIONAL HUMAN EXPERIMENTATION STANDARDS BOARD

The National Human Experimentation Standards Board would be an independent agency in the executive branch of the Government. Its members would be appointed by the President by and with the advice and consent of the Senate.

The members of the Board would be persons of demonstrated knowledge, education, and experience in the field of clinical investigations. Each member would serve for a period of 3 years and would be eligible for reappointment for one additional term.

The members of the Board would be authorized to appoint personnel, and fix the compensation of the personnel in accordance with the provisions of title 5 of the United States Code.

The Board would make the rules which would govern its functions, and have the right to delegate authority.

Experts and consultants could be made available, under the terms of section 3109 of title 5, United States Code.

The Board could appoint one or more advisory committees to be composed of such private citizens and officials of government at all levels as the Board would deem suitable.

The services and facilities of other agencies of Government would, with their consent, be called upon. Other services of a voluntary and uncompensated nature could be accepted by the Board, notwithstanding the provisions of section 3676 of the revised statutes, and unconditional gifts of services or property could be accepted as well.

The Board could enter into contracts or agreements with other public or private nonprofit entities to conduct studies as required by the provisions of this act.

The Federal agencies are authorized and directed to make available to the Board whatever services or information the Board requests, insofar as practicable.

The Chairman and members of the Board would be compensated, respectively, at levels 3 and 4 of the executive pay schedule.

The Board would have subpena powers, and the right to hold hearings. Those who conducted experiments and failed to respond to the Board could be held in contempt of court.

The Board would establish national guidelines for human experimentation in those projects financed by Federal funds. Any experiment could be reviewed in its formulative stages to insure its compliance with the guidelines.

Where experiments already underway are found not to comply with established guidelines, the Board could obtain an injunction to discontinue the experiment and could compensate any victims of the experiment.

The Board would submit an annual report to the President which would be transmitted to the Congress with recommendations regarding legislation.

93d CONGRESS
1st Session

S. 934

IN THE SENATE OF THE UNITED STATES

February 21, 1973

Mr. Humphrey introduced the following bill; which was read twice and referred to the Committee on Government Operations

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A BILL

To establish within the executive branch an independent board to establish guidelines for experiments involving human beings.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act shall be known as the "National Human Experimentation Standards Board Act".

ESTABLISHMENT OF BOARD

Sec. 2. (a) There is hereby established, as an independent agency in the executive branch, a National Human Experimentation Standards Board (hereinafter referred to as the "Board").

(b) The Board shall be composed of five members to be appointed by the President by and with the advice and consent of the Senate from among individuals who by virtue of their service, experience, or education are especially qualified to serve on the Board. The members shall select a Chairman and a Vice Chairman from among their membership. The terms of office of each member of the Board shall be three years except that—

(1) the members first appointed shall serve, as designated by the President, one for a term of one year, two for a term of two years, and two for a term of three years;

(2) any member appointed to fill a vacancy shall serve for the remainder of the term for which his predecessor was appointed; and

(3) a member shall be eligible for reappointment for one additional term.

(c) Any vacancy on the Board shall not affect its powers and three members of the Board shall constitute a quorum except that the Chairman may prescribe a lesser number to constitute a quorum for the purpose of conducting hearings.

(d) Members should be chosen from persons who are representative of the fields associated and concerned with clinical investigations.

ADMINISTRATIVE POWERS

Sec. 3. (a) In order to carry out the provisions of this Act, the Board is authorized to—

(1) appoint and fix the compensation of personnel of the Board in accordance with the provisions of title 5, United States Code;

(2) make, promulgate, issue, rescind, and amend rules and regulations as may be necessary to carry out the functions vested in the Board and delegate authority to any officer or employee;

(3) employ experts and consultants in accordance with section 3109 of title 5, United States Code;

(4) appoint one or more advisory committees composed of such private citizens and officials of Federal, State, and local governments as it deems desirable, to advise it with respect to its functions under this Act;

(5) utilize, with their consent, the services, equipment, personnel, information, and facilities of other Federal, State, and local public agencies with or without reimbursement therefor;

(6) accept voluntary and uncompensated services, notwithstanding the provisions of section 3676 of the Revised Statutes;

(7) accept unconditional gifts or donations of serv-

ices, money, or property, real, personal, or mixed, tangible, or intangible;

(8) take such actions as may be required for the accomplishment of the objectives of the Board; and

(9) make contracts with public or private nonprofit entities to conduct studies related to the purposes of this Act.

(b) Upon request made by the Board, each Federal agency is authorized and directed to make its services, equipment, personnel, facilities, and information (including suggestions, estimates, and statistics) available to the greatest practicable extent consistent with other laws to the Board in the performance of its functions with or without reimbursement.

(c) Each member of a committee appointed pursuant to clause (4) of subsection (a) of this section who is not an officer or employee of the Federal Government shall be compensated at the rate prescribed for GS–18 under section 5332 of title 5, United States Code, for each day he is engaged in the actual performance of his duties (including traveltime) as a member of a committee. All members shall be reimbursed for travel, subsistence, and necessary expenses incurred in the performance of their duties.

(d) (1) The Board or any duly authorized subcommittee or member thereof may, for the purposes of carrying out the provisions of this Act, hold such hearings, sit and act at such times and places, administer such oaths, and require by subpena or otherwise the attendance and testimony of such witnesses and the production of such books, records, correspondence, memorandums, papers, and documents as the Board or such subcommittee or member may deem advisable. Any member of the Board may administer oaths or affirmations to witnesses appearing before the Board or before such subcommittee or member. Subpenas may be issued under the signature of the Chairman or any duly designated member of the Board, and may be served by any person designated by the Chairman or such member.

(2) In the case of contumacy or refusal to obey a subpena issued under paragraph (1) by any person who resides, is found, or transacts business within the jurisdiction of any district court of the United States, such court, upon application made by the Attorney General of the United States at the request of the Chairman of the Board, shall have jurisdiction to issue to such person an order requiring such person to appear before the Board or a subcommittee or member thereof, there to produce evidence is so ordered, or there to give testimony touching the matter under inquiry. Any failure of such person to obey any such order of the court may be punished by the court as a contempt thereof.

COMPENSATION

SEC. 4. (a) Section 5314 of title 5, United States Code, is amended by adding at the end thereof the following new paragraph:

"(59) Chairman, National Human Experimentation Standards Board."

(b) Section 5315 of title 5, United States Code, is amended by adding at the end thereof the following new paragraph:

"(96) Members, National Human Experimentation Standards Board (4)."

FUNCTIONS

SEC. 5. (a) It shall be the function of the Board to—

(1) establish guidelines for the involvement of human beings in medical experiments which are funded in whole or in part with Federal funds;

(2) review all planned medical experiments that involve human begins which are funded in whole or in part with Federal funds to determine if the guidelines established under paragraph (1) are being complied with;

(3) obtain an injunction to prevent such experimentation in a case where such experiments are found not to comply with established guidelines;

(4) provide for the compensation of victims of experiments that do not meet the established guidelines; and

(5) prepare and submit an annual report to the President, for transmittal to the Congress, recommending legislation, if required, and detailing the performance of the Board during the preceding year.

FDA
NOVEMBER 1971
DRUG BULLETIN

DIETHYLSTILBESTROL CONTRAINDICATED IN PREGNANCY

DRUG'S USE LINKED TO ADENOCARCINOMA IN THE OFFSPRING

We wish to bring to the attention of all physicians, hospitals, and medical personnel an important possible toxic effect of diethylstilbestrol reported for the first time in April 1971 by Herbst, et al[1]. From their studies the authors concluded that maternal ingestion of diethylstilbestrol during pregnancy appears to increase the risk of vaginal adenocarcinoma developing years later in the offspring exposed. The authors studied eight cases of adenocarcinoma of the vagina in patients born between 1946 and 1951. The malignancies were identified and treated between 1966 and 1969. In seven of the eight cases, there was a history of maternal use of diethylstilbestrol. Because this type of malignancy in young girls had rarely been reported previously, the authors conducted a retrospective investigation in an attempt to find factors that may be associated with such malignancy in this age group. Four matched controls were established for each patient and the data obtained were subjected to statistical analysis. A statistically significant relationship was observed for three variables: diethylstilbestrol given during pregnancy ($p=.00001$), bleeding in that pregnancy ($p=$less than .05) and prior pregnancy loss ($p=$less than .01). It is obvious that the most significant of the variables is the administration of diethylstilbestrol during pregnancy.

Since publication of this study, five additional cases of this malignancy associated with the maternal use of diethylstilbestrol have been reported by Greenwald, et al[2]. Dr. Herbst, in a recent communication to FDA, has reported an additional 15 cases associated with use of this drug, bringing the total number of known cases to 27. It must be emphasized that this type of epidemiologic study defines only an association and not necessarily a cause-and-effect relationship. Further studies are underway to clarify the significance of these findings.

In the meantime, the FDA is initiating the following precautionary actions:

1. All manufacturers of DES or closely related congeners (dienestrol, hexestrol, benzestrol, promethestrol) are being notified that appropriate changes will be required in the labeling for such drugs. This change will consist in the listing of pregnancy as a contraindication to the use of diethylstilbestrol and the other above-mentioned compounds.

2. All other estrogens will be required to have the following WARNING in their labeling: "A statistically significant association has been reported between maternal ingestion during pregnancy of diethylstilbestrol and the occurrence of vaginal carcinoma developing years later in the offspring. Whether such an association is applicable to all estrogens is not known at this time. In any event, estrogens are not indicated for use during pregnancy."

3. Epidemiological studies are being initiated to determine the true incidence of this disease in young women, the number at risk, the characteristics of patient populations with this malignancy, and the probability of a cause-and-effect relationship.

Both FDA and the medical profession face a responsibility to help determine whether this reported association constitutes a cause-and-effect relationship. We ask that all physicians consider appropriate steps to assist FDA case-finding and to protect any patients who might be at risk.

It may be possible to trace the offspring of those mothers who received DES during pregnancy. All physicians should be especially alert for young women whose mothers may have received hormonal therapy during pregnancy, particularly those young women who may be experiencing irregular vaginal bleeding. The association should be a routine consideration for physicians whose practice includes young women.

This is a previously unsuspected health problem. Further information is essential to the FDA and to the medical profession. We ask your help in reporting any cases you encounter for entry in a case registry.

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1. Herbst, et al – Adenocarcinoma of the Vagina – New England Journal of Medicine – Volume 284, Number 16 (April 22, 1971).

2. Greenwald, et al – Vaginal Cancer After Maternal Treatment with Synthetic Estrogens – New England Journal of Medicine, Volume 285, Number 7, (August 12, 1971).

FDA will take every possible step to insure that you are kept abreast of new information as soon as it can be gathered and analyzed.

For your convenience, an adverse reaction reporting form is printed in this bulletin. FDA will forward a supply of forms to each practicing physician as soon as they are printed. Facsimile forms are acceptable.

DRUG EXPERIENCE REPORT *(IN CONFIDENCE)*			Form Approved OMB No. XXXXXXX
PATIENT INITIALS *(Optional)*			DATE OF REACTION ONSET
SUSPECTED REACTION(S)			
SUSPECTED DRUG(S); TRADE/GENERIC NAME *(Manufacturer's name, if possible)*			
DISORDER OR REASON FOR USE OF DRUG(S) *(Optional)*	ROUTE	TOTAL DAILY DOSE	DATES OF ADMINISTRATION
OTHER DRUGS TAKEN CONCOMITANTLY			
COMMENTS *(Optional)*			
PHYSICIAN'S NAME, ADDRESS, AND ZIP CODE			

FD PROPOSED FORM

Senator **Kennedy**. Tomorrow we will continue the hearings beginning at 10 a.m. The subcommittee stands in recess.

Tomorrow we will continue the hearings beginning at 10 a.m. The subcommittee stands in recess.

[Whereupon, at 2 p.m., the hearing was recessed, to be reconvened Thursday, February 22, at 10 a.m.]

QUALITY OF HEALTH CARE—HUMAN EXPERIMENTATION, 1973

THURSDAY, FEBRUARY 22, 1973

U.S. SENATE,
SUBCOMMITTEE ON HEALTH OF THE
COMMITTEE ON LABOR AND PUBLIC WELFARE,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:05 in Room 1318, Dirksen Building, Senator Edward M. Kennedy, chairman, presiding.

Present: Senators Kennedy and Javits.

Committee staff members present: LeRoy G. Goldman, professional staff member and Jay B. Cutler, minority counsel.

Senator KENNEDY. The subcommittee will come to order.

Today is the second in a series of 6 days of hearings of the Quality of Medical Care and Human Experimentation. Yesterday we learned that a pattern of practice developed in the state of Tennessee with regard to the use of Depo-Provera for purposes not currently approved by the Food and Drug Administration. We learned that in this country a doctor has the freedom to independently overrule the judgment of the Food and Drug Administration with regard to the safety and efficacy of any drug. Anyone of us can, at any time, walk into a doctor's office and receive experimental medication or treatment, without knowing it. And we can only redress our grievances if we are harmed.

Today we will learn of patterns of practice that have developed in this country with regard to DES. Yesterday the Commissioner of the Food and Drug Administration, Dr. Edwards, said that the widespread use of DES in university centers would be of great concern, that concern is justified, and we will demonstrate that today.

DES causes vaginal cancer in the offspring of women who have taken it during their pregnancy. We will hear today that it is also associated with a second type of cancer—cervical cancer, and that it may be associated with additional types of cancer. Given this known carcinogenicity, we have banned DES from cattle feed. We have not banned its use in the treatment of human beings. Only yesterday the FDA approved DES for emergency use as a morning after pill. Today we will try to determine if even that limited action can be justified.

Our first witnesses this morning are Dr. Sidney Wolfe and Ms. Anita Johnson of the Health Research Group.

Ms. Johnson is an attorney, specializing in food and drug safety.

Dr. Wolfe is director of Health Research Group, Washington, D.C.; he is a graduate of Western Reserve Medical School, and formerly spent 5 years as a research physician with the National Institutes of Health.

We are looking forward to your testimony.

STATEMENTS OF DR. SIDNEY WOLFE AND MS. ANITA JOHNSON, HEALTH RESEARCH GROUP, WASHINGTON, D.C.

Ms. Johnson. I am Anita Johnson, an attorney with the Health Research Group in Washington, D.C., and this is Dr. Sidney Wolfe, a physician with the same group.

I wish to insert into the record at the outset a report on the "Morning after Pill" which we released December 8, 1972.

Diethylstilbestrol (DES) has long been known to be carcinogenic in animals and since 1969 has been known to cause cancer in humans administered DES in utero. Last summer FDA banned use of DES in animal feed because there were small residues of the substance in meat intended for human consumption. Although FDA long ago approved DES as a drug for certain circumscribed purposes it has never approved DES for use as a postcoital contraceptive. DES has never been shown to be safe and effective for this purpose.

Under these circumstances, doctors should not administer DES to women, if at all, only under the most stringent and careful conditions. All women should be informed that DES may cause cancer in their offspring if the Morning After Pill is not effective, and that animal tests have shown it causes cancer in animals administered the drug. No doctors should administer the pill unless they have filed an investigational new drug application with the FDA, are engaged in a research study involving meticulous short- and long-term followup of each patient, are under continuous institutional peer review of the experiment, keep complete records, and administer the drug only to patients who are fully informed of the risks of the experiment. Use of the Morning After Pill cannot even arguably be justified unless in the context of a well-designed and well-protected research study.

Yet the DES Morning After Pill is widely used. In cases we know about, it is used with unacceptable carelessness, in some cases without even the most elemental requirements of a genuine experiment.

Advocates for Medical Information, an Ann Arbor student group, reported to us last November that the health service at the University of Michigan was dispensing DES like water. At that time, women were not warned of possible side effects other than nausea, or of its unapproved status. Only nine out of the 69 cases studied by Advocates for Medicine Information were followed up, and these were voluntary followups by the patient. Although a family history of breast or genital cancer vastly increases the risk of DES, only three of the women were asked about this. Only 10 stated that their doctors inquired about exposure to other estrogens such as birth control pills or DES in utero. Doctors as a rule did not inquire about the possibility of pregnancy from the prior month—in which case DES would not abort and could damage the fetus—and did not assess the likelihood of pregnancy at the time of prescription.

At the University of Vermont, followup is lackadaisical. "If the woman becomes pregnant," said one doctor, "we assume she will return to the infirmary and tell us." When asked what warnings the women get at the health center, the doctor replied, "We don't dwell on the risks because one-shot use of DES presents no risk to the woman." Even if the woman becomes pregnant after DES use, she is not told of the evidence of risk to the fetus. Doctors there do not check the medical or family history of the woman for evidence of increased risk, "because the pill doesn't generate problems."

At the University of Oregon, the health service director stated that women are informed about the risk of cancer to female offspring, and are questioned about their family history before the pill is dispensed. There is no formal followup. "If she's had unprotected intercourse and asks for the pills, she gets it unless she has the counter indications," the director said.

At Oregon State, the health center gynecologist does not believe that DES is a proven human carcinogen. "I tell the women that Ralph Nader believes DES is dangerous, but that I don't." Women are not asked for family histories of cancer, and they are dispensed the pill for any unprotected intercourse. Asked whether the women are informed that it is an unapproved use, the doctor stated: "We tell the girls that FDA is studying DES."

At Indiana University the health service has prepared a written informed consent form which states that because of a strong possibility of cancer in offspring, "it is probably unwise to continue pregnancy" if DES is not effective. The form states that DES has not been approved for this use, that the long term and some of the short term effects of the pill are not known, and that the use of well studied methods of birth control is preferable. This consent form has only been available since December 14, 1972. Physicians there use the form only at their option. One doctor said that women are checked to be sure they are not already pregnant, and are discouraged from taking DES if their chances of pregnancy are not great. The Indiana Public Interest Research Group reports that at least one woman was given DES in 1972 with none of the above cautions except that she was informed that it was experimental.

At Princeton University women are apparently warned that their offspring may get cancer, but they are not warned of a risk to themselves, are not told that the pills are experimental, and are not asked for family histories.

Scripps College in California has dispensed the Morning After Pill with no warnings but that of nausea, with no medical or family histories or other inquiries made. At Tufts and Boston Universities, the pill has been dispensed with no cancer warnings given. At UCLA, health service doctors told the L.A. Times that histories were taken and followup made, but a student there reported she had been given no cancer warnings.

At Syracuse, DES is dispensed. There are no regulations on dispensing DES, and no records are kept. At the request of the Syracuse Public Interest Research Group, the director agreed to issue a fact sheet to women who requested the pill. At Toronto, women are counseled to have an abortion if they become pregnant. and told that DES should not be used for routine contraception. At Cal State, a reporter was told that "universal procedures" were followed.

Other centers distributing the Morning After Pill are Minnesota, Harvard and Iowa State, and the Feminist Women's Health Center in L.A. Here in Washington, our Office manager was able to get a prescription for the Morning After Pill over the phone with no questions asked and no warnings given.

Senator JAVITS. Madam Witness, would you mind yielding to me for 30 seconds, with the chairman's permission.

I dislike, Mr. Chairman, to interrupt, but I must leave and wish at this time to introduce for the hearing record my preliminary statement relating to my own bill on protection of human subjects in experimentation and my bill to stimulate medical school concern with the problem which I shall introduce today with Senators Williams and Mondale.

I want to compliment the chairman upon very promptly getting into this question which is very, very much before the country this morning. I assure you as always of my close cooperation in the work of this subcommittee on this subject.

Senator KENNEDY. Thank you very much.

Senator JAVITS. Thank you very much. I am sorry to interrupt.

STATEMENT OF HON. JACOB K. JAVITS, A U.S. SENATOR FROM THE STATE OF NEW YORK

Senator JAVITS. As the Health Subcommittee of the Committee on Labor and Public Welfare (of which I am ranking minority member) begins hearings on such issues as psychosurgery, organ transplants, genetic manipulations, sterilization procedures for criminal behavior, brain-washing, mind control and mind expanding techniques, and yes, even the very concept of birth and death itself, the urgent need to adequately protect the rights and welfare of human subjects in all research activities becomes imperative.

To assure meaningful legal controls of all federally supported research activities involving human subjects, I have introduced the "Protection of Human Subjects" bill, S. 878.

The bill is patterned upon NIH research guidelines and outlines flexible operating procedures which can be adapted to a variety of federally funded grant and contract mechanisms to safeguard the rights and welfare of human subjects.

There is no doubt but that we must constantly and continually encourage research into the great enigma of man and his world if we are to eventually overcome the abysmal depths of ignorance and disease.

But we must guard against self delusion lest it harm that precious quality of life which is so uniquely human—also to be humane. Scientific inquiry must constantly be blended with judgment, compassion and sympathy, the true synthesis of humaneness and humanity.

The dilemma of what reforms should be imposed upon scientific inquiry and medical experimentation will require the leadership of the medical profession. The recent book, *Research on Human Subjects—Problems of Social Control In Medical Experimentation*, by Bernard Barber, John J. Lally, Julia Loughlin Makarushka, and Daniel Sullivan, unfortunately concludes that medical schools ". . . have not been ethical leaders with regard to peer group review.

They have a proud record of scientific leadership, but their record in ethical innovation is not distinguished".

Medical schools have primary responsibility for the education and training of those who will carry on the medical profession as practitioners, as researchers, and as teachers, and are the natural environment to become ethical leaders in respect to efforts to safeguard the rights and welfare of the human subjects of biomedical research.

I believe that unless significant improvement is made in the curricula of our medical schools—to provide ethical leadership in protecting and safeguarding the rights of human subjects—it will augur ill for our nation's future. Therefore, I am introducing with Senator Williams, Chairman of the Committee, a bill to authorize special project grants to medical schools to stimulate the development of programs in the ethical, social and legal implications of the advances in biomedical science and technology, with emphasis upon their implications for individuals and society.

It is imperative that we maintain a constant vigil lest the zeal which first motivated and then impelled man forward in his never-ending quest for enlightenment be like the sorcerer's apprentice, exceeding its bounds and unfettered, cause us to outdistance our own capacity for the best values of humanity; and this could easily result in moral suicide.

At the same time, excessive rigidity in the regulation of human subject experimentation because of some improprieties in ethical self regulation would, I believe, be to the disadvantage of the individual and society. Civilized society cannot tolerate the callous disregard of human rights for any purpose and mankind would be badly served if we write rigid laws to govern research practices and scientific investigation; but research, development and the reduction to practice of new ideas are not carried out in a practical, ethical, or legal vacuum and the public interest would not be served by such an inflexible approach.

In view of my own deep personal concern about this subject, I have sponsored—with the Chairman of the Labor and Public Welfare Committee, Senator Williams; the ranking minority member of the Health Subcommittee, Senator Schweiker; and the Chairman of the Health Subcommittee, Senator Kennedy—a special Congressional briefing session on February 27 about the advances in biomedical science and their important consequences for the future of mankind generally, and for our country in particular. These new developments have profound ethical and legislative implications, and so require understanding on our part as legislators if they are to be used for maximum benefit to our people.

Senator KENNEDY. Thank you, Senator Javits.

Ms. Johnson would you please continue your statement.

Ms. JOHNSON. Thank you, Senator Kennedy.

The cases I have cited are but a few examples of how DES was used as the Morning After Pill while it was still unapproved for such use due to lack of evidence of safety and efficacy.

If the situation was deplorable at many college campuses then, what will it be like now that the FDA has proposed approving its use? Reliance on peer review and institutional review to delimit administration of the pill without information consent and other precautions, as proposed by the FDA, will certainly not work for an approved drug if it did not work for the same drug while it was "experimental."

If peer review and institutional review alone would suffice, why did the following occur:

1. Not one university health service in the United States filed an IND to use DES as the Morning After Pill and almost none collected data appropriate for such human experimentation.

2. On many campuses, there was and still is no uniform policy on what information needs to be given to women in order to fulfill conditions of informed consent. It was "left up to the individual physician" to decide what the patient should be told.

3. At one university, the Institutional Peer Review Committee was not even asked by health service doctors whether or not the health service should participate in proposed NIH studies to test out two other estrogens as morning after pills. The Committee was told the health service doctors would participate.

Just as peer review alone has and will continue to fail to curb unnecessary surgery and other therapeutic excesses of doctors, so too, unaided by informed patients, will it provide proper surveillance over the use of DES or any other drug.

Whether as an unapproved drug or, imminently as an approved use, if FDA continues to allow the use of DES as a Morning After Pill, the following conditions should apply:

1. The physician should participate in a well-designed study, so that reliable information about the drug will increase, to help offset the risks to the voluntary subject.

2. Before a doctor can prescribe the Morning After Pill he should be required to give to the patient the following statement:

(*a*) DES has not been proven 100 percent effective for use as a Morning After Pill. It has been found to cause cancer in the offspring of some of the women who have taken it. If the Morning After Pill does not prevent pregnancy, you should have an abortion.

(*b*) Animal tests have shown the DES can cause cancer in the animal taking the drug.

If you have ever had breast or genital cancer, you should not take this drug. If your family has a history of breast or genital cancer the risk of danger to you is increased. The risk is probably higher if you have been exposed to other estrogens, such as birth control pills or DES administered to your mother while you were a fetus.

(*c*) Your doctor will determine as nearly as possible whether you are pregnant from a prior intercourse. If so, you should not take DES. He will also try to determine whether you are likely to have been fertile at the time of this intercourse.

(*d*) If you have read this statement and have decided to take the Morning After Pill, please sign here and give this section to your doctor.

(*e*) DES should not be used as a routine form of birth control. Do not take it if you have taken it before. Do not take it again.

This statement resembles the labeling of the drug. It should be given before the prescription is made, as is labeling on all consumer products other than drugs.

This statement should be signed by the patient before the doctor writes the prescription.

Some of the characteristics which make guinea pigs (or other experimental animals) most suitable for experimentation is the fact that they are captives and they do not need to be told what you are doing, nor need their permission be asked.

Whether the subjects are prisoners, college students, military personnel or poor people, they share a common sense of captivity and the use of any drugs on them must be regulated with paramount regard for their well-being.

Not only must existing legislation governing non-marketed drugs be implemented but new legislation to govern unapproved uses is sorely needed.

Senator KENNEDY. Dr. Wolfe, do you have any comments you would like to make at this time? If not, I want to get into some questions.

Dr. WOLFE. Just as you have amply demonstrated in your surveys of this country that the quality of medical practice varies from the best to the worst, it is also clear that although the quality of medical practice in some university centers is high, now in some places quite the opposite is true. Thus, one can see a complete spectrum of degrees to which doctors do or do not give the proper amount of information to women about the morning-after pill.

This is the kind of situation that is going to continue until something occurs, probably legislatively, to control so-called unapproved uses of approved drugs.

I would be happy to answer any questions that you have.

Senator KENNEDY. You mention I think some 15 different university medical centers which dispense DES; is that correct?

Dr. WOLFE. Yes.

Senator KENNEDY. Could you tell us about the extent of the use of it in these medical centers?

You refer to different reactions of health centers in given colleges, but how widespread is it in those 15 different areas, based upon your studies?

Dr. WOLFE. There are a couple of answers to that. First of all, one physician who is a consultant to NIH, which is currently giving out contracts to study the use of other estrogens for the morning after pill, has estimated that approximately 2 million women have gotten the morning after pill.

When you get down to the level of the individual university, a number of universities for a number of years have been giving the morning after pill out to as many as 400, 500, 600 women per year. In fact, one of the prerequisites that the NIH demands of institutions that are participating in its new studies on the use of estrogens for the morning after pill is that they treat at least a couple hundred women a year.

There were a few schools in our surveys in which it was only given DES out to five or ten women per year, but I believe many more have given it to several hundred per year.

Senator KENNEDY. So it is your testimony that at least in these 15 medical centers, DES is being distributed; that the extent of the distribution varies from university center to center; and that patterns of informed consent vary extensively.

Dr. WOLFE. From none to a very complete set of information.

Senator **Kennedy**. Do you think these are the only 15 university centers in the country that are doing it? Is this an exhaustive list?

Dr. **Wolfe**. No. This is by no means exhaustive. It was accumulated in part in response to the localization of the "Morning After Pill" report of December 1972 which we would like to enter into the record, and some information was also accumulated by the public interest research groups on various college campuses.

Senator **Kennedy**. That may be put in the record.

[The information referred to follows:]

HEALTH RESEARCH GROUP REPORT ON
THE MORNING AFTER PILL
December 8, 1972

INTRODUCTION

As of this time, approximately 100 American women are known to have developed vaginal cancer as a result of ingestion of diethyl stilbestrol by their mothers while they were pregnant. Most of these women are being operated on to arrest further spread of the cancer. If detected early enough they will live. Others have and will continue to die.

Tens of thousands of women were exposed during the 1940's and 1950's to large doses of DES prescribed by doctors to prevent miscarriage. Although the fact that 100 daughters of these women are already known to have developed vaginal cancer is a testimony to the lack of safety of the drug, the well-documented lack of effectiveness in preventing miscarriages (the use for which it was given to mothers of cancer victims) makes the situation even more appalling.

As early as 1953, Dieckman published a study which cast serious doubt on the efficacy of DES in preventing miscarriage. (Am. J. Ob. Gyn. 66) In a review of the existing studies on this use in 1958, Goldzieher (Am. J. Ob. Gyn., 75, 12C2) concluded that "there is no statistical evidence for the value of stilbestrol therapy."

In testifying before Congress, FDA Commissioner Edwards could point to no scientific evidence that it was effective. He said lamely that there must be some evidence "because of its widespread use in the medical profession."

Whether chloramphenicol for treating acne, penicillin for the common cold or DES to prevent abortions the problem is much the same. Widespread use by the medical profession is very often widespread misuse.

Thus, DES, given in large doses to women in the 1940's and 1950's without evidence of efficacy, has caused cancer in a generation of women in the 1960's and 1970's (possibly 1980's and 1990's). As a result of this, the FDA has begun, albeit slowly, to ban DES from the food supply.

The story of the Morning After Pill gives chilling witness to the recalcitrance of the FDA, the medical profession and the drug industry to learn from tragic experiences.

According to an official in the Center for Population Research of the National Institutes of Health, "Most university health services are giving the Morning After Pill". The Morning After Pill is given to women to prevent pregnancy after they have had unprotected intercourse while potentially ovulating. The Morning After Pill is a massive dose of diethyl stilbestrol, (25 mg) given twice a day for five days.

The November 1971 FDA Drug Bulletin warning all physicians against use of DES in pregnancy has, according to many obstetricians, significantly decreased its use to prevent miscarriages. Despite this, however, sales of DES for 1972 increased over 1971. Total DES sales for 1971 were $1,844,000. (price to manufacturer). 9 month figures for Lilly, the major supplier, (as it is for DES used in animal feed) were up 4% from last year.

Whether the increase in total sales despite an apparent decrease in one usage is due to increased popularity of the Morning After Pill generated by an October 1971 J.A.M.A. report of Kuchera is unknown. What is known, however, is that more of this potent carcinogen is being given than before.

This report presents evidence of the irresponsible way in which DES is now being used as the Morning After Pill on the college campus and by the private practitioner. Unlike the use of DES to prevent miscarriage, which was at least an approved use, although dangerous and ineffective, the current use is unapproved. The FDA again watches idly while another possible tragedy unfolds.

HAZARDS OF DES (And other estrogens)

In addition to the unfortunate human evidence of carcinogenicity of DES given during pregnancy to women whose daughters then developed cancer 10 to 20 years later, there are other possible hazards of not only DES but all estrogens.

1. Dr. Arthur Herbst, whose April, 1971, New England Journal article lifted the lid off this disaster has said, in response to Congressional inquiry about how much and how long does DES have to be taken to be carcinogenic,

> "We do not have enough data or knowledge at the present time to say what the smallest dose or the shortest duration of exposure to this drug is that could cause trouble."
> (DES Hearings 11/71, p. 8)

This answers those who say the Morning After Pill is not given for a long enough period of time to be carcinogenic.

2. Both Dr. Roy Hertz of Rockefeller University and Dr. Mort Lipsett of the National Institutes of Health, experts in hormonal cancer, have repeatedly stated that the best available information suggests that all estrogens given at comparable doses and for comparable periods of time as DES would cause the same carcinogenic effects.

This is in sharp opposition to those who would replace DES with natural estrogens for use as a morning after pill. The Center for Population Research of the NIH is currently awarding contracts to University Health Services and family planning agencies to "test out" the effectiveness of natural estrogens as a morning after pill, hoping to get people to change from DES and ultimately "to get the label changed for indicated uses of natural estrogens to include the post-coital contraception". (Morning After Pill)

3. There is an increased incidence of breast cancer in women with family histories of this disease (Cancer Research 23, 1503, 1963). In addition, it is generally known that estrogens are contraindicated in anyone with breast cancer.* Further, "breast cancer exists in some cases for years before it can be clinically detected... We have no data concerning the effect of such medication (estrogens) on breast cancer during the developmental or pre-clinical phase of the disease. (Hertz, DES Hearings 11/71, p. 62)

This is a challenge to those unthinking or ignorant doctors who would give the Morning After Pill (or, for that matter, any estrogen) to women without taking a family history.(See later part of report for evidence of this at the University of Michigan Health Service and in Washington, D.C.).

4. In the same hearings, Dr. Hertz, also stated,"Actually, our inadequate knowledge concerning the relationship of estrogens to cancer in women is comparable with what was known about the association between lung cancer and cigarette smoking before extensive epidemiologic study delineated this overwhelmingly significant relationship."

He continues, "Addition of any artificial estrogen beyond the natural estrogen produced in the body disturbs a natural balance which, even under ideal natural conditions is precarious, demonstrated by the fact that one of each 16 women will develop breast cancer during her lifetime." (In point of fact, the amount of DES given daily as a Morning After Pill is about 500 times that produced daily in the body). (Lipsett, DES hearings, Nov. 1971, p. 33)

These latter statements, coupled with the known animal carcinogenicity of estrogens (mice, rats, rabbits, dogs, and hamsters -- a variety of organs including breast, uterus, ovaries, kidney) counter those who argue that the only danger of the Morning After Pill is for the foetus and, since i is 100% effective as an abortion-promoter when given less than 72 hours after intercourse, there will be no foetus so why worry. Aside from the fact that the Morning After Pill is less than 100% effective in aborting (see below) the woman herself may be at risk.

In summary, the known human carcinogenicity of DES in offspring and the larg number of animal studies showing direct effects identify this and other estrogens as potentially hazardous. The next section describes human experiments which were and are being done to study the effectiveness of the Morning After Pill, rather than its safety.

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* premenopausal women

EFFICACY OF THE MORNING AFTER PILL:
Safety and Efficacy of Doctors Prescribing it

The careful work of Morris et al in New Haven (Am. J. Ob. Gyn 96, 804, 1966) established the basis for using synthetic estrogens as a morning after pill. However, the work of Kuchera, at the University of Michigan Health Service, (J. Am. Med. Assoc. 218, 562, 1971) published in October, 1971, (one month before the FDA warned all U.S. doctors not to use DES during pregnancy) drew national attention to this use. One thousand women of child bearing age who were given DES within 72 hours of sexual exposure were reported. There were no pregnancies.

This latter fact is remarkable, if not questionable, for several reasons.

1) Morris has reported several cases in his series of failure of the pill to abort.

2) In a study being conducted by Dr. Joseph Massey of the University of Pennsylvania (See 11/71 DES Hearings, p. 52), 4 of the patients became pregnant.

> Although these pregnancies have been "explained away" by FDA officials as due to previous pregnancy (from the month before) or inadequate dosage -- the fact remains that 4 pregnancies occurred and thus, possible cases of vaginal cancer.

3) The absence of stating "1000 consecutive cases" in the paper implies that some of the women may have been lost to follow-up. This would not be surprising since about 1/3 of the women in the Massey study (although they were rape victims) were lost to follow-up. It is even less surprising when considering more recent information from women at the University of Michigan, collected from the women given the pills after Dr. Kuchera's study was over. About 3/4 of the 69 women responding to the survey were not followed up at all.

It is difficult to believe that there was 100% followup during the study period and only 25% followup after. For all these reasons, there is considerable doubt as to the 100% effectiveness touted by Kuchera for the Morning After Pill. Did some of those who may have dropped out of the study become pregnant?

Estimates are that 1/50 to 1/25 of women given the Morning After Pill are actually pregnant. (Fertil. Steril. 1:485:488, 1960) Thus, if 4 pregnancies occur in a group of 500 given the pills, the failure rate is much higher than it might seem. Of the 500, only 10 (using the 1 out of 50 figure) would become pregnant without the pill. If 4 get pregnant with the pill, the effectiveness is only 60%.

Unless adequately warned about the known carcinogenicity of the pills for the foetus, the women who become pregnant will not have the proper informed impetus to have a therapeutic abortion. That little information is given to them is seen in the results of the survey at the University of Michigan.

Advocates for Medical Information in Ann Arbor, Michigan, conducted a survey of 69 women who were given the Morning After Pill, most of them at the University of Michigan Health Service. Although most of the women were warned that DES might cause nausea, only five were warned about a cancer hazard to their offspring. None were informed of a suspected cancer hazard to themselves.

Doctors who prescribed DES asked only three of the women their family medical histories, in spite of the fact that a family history of genital or breast cancer is a known contraindication for the approved use of DES. Only four women out of 64 were given pregnancy tests or questioned about possible pregnancy from previous intercourse before being given DES, although DES could not end such pregnancies and could cause cancer in the fetuses. Only ten women were questioned about other personal exposure to estrogens, such as birth control pills.

Advocates for Medical Information found that most women were not informed that the Morning After Pill was an unapproved use. Only seven women were so informed.

Over 75% of the women given DES were not followed up at all, either for short-range side effects or even to see if they had become pregnant.

This survey gives reason for the concern that the use of DES as a Morning After Pill may be becoming much less cautious (from the standpoint of the doctors giving it out) than it was when the original studies were done.

Our own limited investigations showed that prescriptions for the Morning After Pill are obtainable in Washington by phone. A doctor recommended by a public pregnancy counseling service agreed to prescribe it with no questions whatsoever about the patient, and no warnings about the risks.

Most planned parenthood offices in Washington, D.C. and other U.S. cities do not give out DES themselves, since their National Medical Department stated last year, "The technique of post-coital contraception using stilbestrol (DES) or dienestrol can not be considered to be an appropriate method of contraception." However, personnel in the offices queried did not know the reasons for this policy, and led us to the same doctor mentioned above.

What has the FDA done? One year ago, at the DES Hearings, Dr. Edwards stated, "We are including in a forthcoming drug bulletin a statement that although the use of DES post-coitally is fairly widespread, the FDA regards this use as investigational and is currently reviewing data to determine the safety and efficacy for this use." *

When asked at the same hearings, "Is there a special urgency that FDA require that all investigational work on this drug be strictly controlled? Dr. Edwards said, "Yes, no question about it."

Although there was no question about the special urgency for FDA action in November 1971, one year and countless exposures later, FDA has taken no action whatsoever to control the Morning After Pill.

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* This statement was never included in the drug bulletin on DES.

RECOMMENDATIONS FOR ACTION

It is clear from the above that widespread and totally uncontrolled use of DES as a morning after pill is a serious problem, with possibly heavy--although unknown---consequences for the public health. The drug industry, the FDA, and the doctors must act to prevent this abuse.

1. The drug manufacturers bear a major part of the responsibility for DES misuse. Without the expense of filing an IND, or paying doctors and patients to participate, Lilly Squibb, Merck, Upjohn and others reap the rewards of unapproved uses of DES. Drug companies can no longer wink an eye at misuse of their products.

   a. Drug companies should be urged to send a "Dear Doctor" letter to all physicians telling them that postcoital contraception is not an approved use of the drug because it has not been proven safe and effective as required by law. Drug detailmen should impress this upon physicians they visit. It is time for the detailmen to become an agent of improving national medical practice, not a promotion pusher.

   b. Drug companies should supply DES to buyers such as University Health Services and Planned Parenthood (which are obviously not using it for the common approved use in postmenopausal women) only when the doctors document that they protect patients by observing standards of informed consent and strict experimental design.

2. FDA should forbid prescribing DES for unapproved uses unless the doctor agrees to abide by its rules of conduct for investigational new drugs. The doctor should not be allowed to subject the patient to unapproved drug uses unless involved in a controlled experiment, which assures society that the amount of information on the drug will increase.

   FDA should require all DES labeling and advertising to contain the warning:

   > The use of DES as a post-coital pill is unapproved since it has not been proven safe and effective for this purpose.

3. Doctors should prescribe the Morning After pill only if involved in a study with the protections the IND regulations afford. Experiments require a six week follow-up to see whether DES prevented pregnancy, and continuous scrutiny by the institution where they are conducted. Doctors prescribing the drugs should have appropriate qualifications to evaluate use of the drug. Complete records must be kept. Provision must be made for long-term follow-up, since cancer has a latency period of 10 years or more.

Before prescribing the pill, the doctor must determine:

1. whether the patient's mother was given DES during her pregnancy.
2. whether there is a background of chronic exposure to DES from birth control pills, and/or other sources.
3. whether the patient has a history of menstrual disorders or other indications of hormonal imbalance.
4. whether there is a family history of genital or breast cancer.
5. whether the patient is already pregnant from prior intercourse.
6. whether the patient would be willing and able to have an abortion should the pill fail to work.

Doctors must fully inform the patient that the drug use is unapproved, and fully inform her of the risks. Doctors who often see patients distraught with fear of pregnancy are reluctant to warn of cancer, because it is never certain and always decades away. It is, however, no longer acceptable to avoid fully informing patients on the basis that the facts will "scare" them or "unnecessarily worry" them. Important life decisions are involved with the morning-after pill, decisions which can be made not by the doctors but by the women themselves.

Dr. WOLFE. I think the 2 million figure bespeaks the fact that in probably at least on half if not more college campuses it is being given out.

Senator KENNEDY. Your belief is that approximately half the colleges——

Dr. WOLFE. At least; right.

Senator KENNEDY. Do you have some additional information on Michigan?

Dr. WOLFE. Yes. We have learned just in the last couple weeks some new information about the University of Michigan study. I think this is important because one of the factors that was most contributory toward increasing the use of the morning after pill was the paper that was published in October of 1971 on the basis of supposedly 1,000 women who were given the morning after pill at the University of Michigan, none of whom allegedly became pregnant.

The NIH sent a team to look at the actual data from this study and has just reported some of these findings.

First of all, it was not given out to just 1,000 women consecutively. We suggested in our December report on the morning after pill that something seemed a bit unusual about their study, because since almost everyone who had used the pill had stated a few pregnancies occurred, it seemed unlikely in 1,000 cases, if they were consecutive, no pregnancies would have occurred.

In fact, it was given out to 1,400 women. In addition, 112 of these women were lost to followup. On a college campus it is highly likely that some of the women lost to followup may have become pregnant; we do not know.

Eighty-one of the cases did not meet the criteria for the study.

I think the most important figure is that six pregnancies did occur.

This may seem a low figure, six pregnancies out of 1,300 women given the pill, but I think that another fact needs to be interjected.

According to statisticians who have looked at the question as to how many women would become pregnant if not given any kind of protection, the answer is that if a woman had unprotected intercourse and did not get the morning after pill, only one in 50 to one in 25 would become pregnant anyway.

In other words, the range of time during which they actually give the morning after pill is such that only one in 25 would become pregnant.

If this is so, out of 1,300 cases, had they not been given the morning after pill, only 52 pregnancies would have occurred. This means that if only 52 pregnancies would have occurred without the use of the pill, and in fact six pregnancies occurred with the use, the failure rate for the pill is approximately 11 percent.

The main point is that it is not 100 percent effective, and I think the myth of 100 percent efficacy which was widespread has misled a lot of institutions into giving out no warnings about fetal carcinogenicity.

If you think it is 100 percent effective, there is no reason to inform a woman she should have an abortion if she becomes pregnant. I think this information about fetal carcinogenicity needs to be given to every potential user. Since the pill isn't 100 percent effective.

Senator KENNEDY. Dr. Edwards testified yesterday that he thought in emergency situations, it may be jusified to use DES. Do you have any opinions about that?

Dr. Wolfe. I think first of all it depends on how you define the emergency situation. Rape is a cruel situation, and as I believe was mentioned yesterday, incest, is also. Situations where there is mental distress are harder to define.

I think that it would be foolish to deny the fact that any woman who comes in for the morning after pill because she is afraid of pregnancy is in some condition of mental stress. I do not think that when all is said and done we *have* really redefined its use.

I think what is of more concern are statements that were made by the FDA about reliance on institutional and peer review to monitor the use of the pill. I think if you look at past experience the data, presented by Ms. Johnson at a time when the morning after pill is still unapproved, at the way in which it was given out, and at the way in which the institutional peer reviews malfunctioned, what do we have to look forward to after it becomes approved?

I think it is extremely important to note that of all the universities that have dispensed the morning after pill, in the 15 we report, and in probably hundreds of others, not one single university in the entire United States ever bothered to submit an investigation on this all new drug application to the FDA. New use of the drug.

In addition, the lack of uniformity of what a doctor had to tell a woman—the head of one university health services said, "I don't tell the doctors what to do. If one of them wants to tell a woman something, that is fine. I leave it up to the doctor."

It is left up to the individual doctors, even within the university health centers.

I think institutional peer reviews are a fine idea, but looking at the health care system in this country, it has not exactly improved in quality very much just on the basis of institutional peer review, and I think just as we always insist that consumers always be involved in other aspects of improving health care, here too it would be appropriate for college students to be sitting in on the panels of institutional review.

Under those circumstances I think one might have a better control of the use of the morning after pill and other drugs on college campuses.

Senator Kennedy. Is there any present mechanism that you are able to determine to require appropriate followup at these university centers?

Dr. Wolfe. I think one of the most often cited statements by people at the FDA is that they do not regulate doctors; "We just regulate drugs." If they really regulated drugs properly, I would be happy.

I think that they frequently back off from doing things which are really regulating drugs under the guise of saying would be regulating doctors.

What do we mean? Under existing legislation they really cannot require every single institution which uses the morning after pill prior to its approval to file an investigational new drug application. As the FDA stated in a letter to all American doctors last year, it would be nice—to paraphrase what they said—for someone who is going to use a drug for a non-approved use to submit an investigational new drug form, but it is not required.

For some reason the law has differentiated between unapproved uses of drugs which are approved for another purpose and drugs which are totally unapproved.

I would submit that the separate indications of a drug should be treated as separate drugs.

For example, in the case of DES, one of the earliest uses involved a woman past menopause who needed estrogen in small amounts. This is an entirely different situation. The safety and efficacy considerations are entirely different than for instance, pregnant women who were taking it to prevent miscarriage, or in this case for women who are taking it as a drug to prevent pregnancy.

So in each case the separate determination of safety and efficacy should be made. By definition, when you say a drug is unapproved, it means they have not determined its safety and efficacy.

If it is going to be used on a woman, in an experimental setting, a number of precautions have to be taken, both to protect the woman's rights, namely, informed consent, and to protect her health, namely, giving her adequate precautions and warnings.

Moreover, a mechanism must function to insure that additional data will be collected. Because, lacking evidence of safety and efficacy, more information needs to be collected in an objective, scientific way to determine eventually whether it should be approved or disapproved.

So I think that any legislation which falls short of treating separate indications in a sense as separate drugs, requiring in every case IND's for each use (investigational new drug applications) be submitted, and determination of safety and efficacy to be made, will continue to treat college students, prisoners and poor people the usual and constant subjects of human experimentation—as guinea pigs.

Senator KENNEDY. Whose responsibility is it to be sure that doctors are using the drugs in an appropriate fashion?

Dr. WOLFE. I think that one mechanism that we have suggested, and will submit with our testimony, is that rather than depending on a package insert which may never be seen by the woman, but which at best is seen by her after she has already taken the medicine—instead of that require the doctor to the FDA could with some legislative help give out a form which listed all of the informed consent conditions to the woman at the time that she was considering possible use of the pill.

Having read this form, and having signed it, then there would be some evidence of informed consent. There is no reason why a panel of doctors from FDA or other institutions could not work out the details of the form for each drug.

It is now apparent that this has been done on at least some campuses for the morning after pill but why should it be in a random haphazard way?

The same form should be used in every college campus. Every woman should see it, sign it, and make sure she is aware of what the conditions are.

Senator KENNEDY. Who should do it? Is that the Food and Drug Administration's responsibility?

Dr. WOLFE. I think that they currently do a very similar thing. Under the current legislation, under existing legislation for totally unapproved drugs, they do require informed consent, and I see no reason why this cannot be extended to drugs which are approved for one use but unapproved for another.

The FDA can serve as the central agency for monitoring in conjunction with university institutional and peer review groups.

Senator KENNEDY. Do patients have any recourse, those patients who have received drugs for experimental use, other than the malpractice suit?

Dr. WOLFE. I don't believe there is any other recourse, aside from the malpractice suit which in this case could be directed at an institution or the individual practitioner.

The whole malpractice question reflects the frustrations of American patients. There is no other recourse and, given all of the difficulties between doctor and patient, and excesses of therapy, whether it is unnecessary surgery or unnecessary or inappropriate utilization of drugs, medical malpractice is the one legitimized form of protest.

I think we should have other forms that are more rational and that attack the problem at an earlier stage.

Senator KENNEDY. If you have some ideas on that, I would like you to submit them. They would be welcome.

The second witness this morning is Dr. Peter Greenwald, the director of the Cancer Control Bureau of New York State. He is also a clinical assistant professor of medicine at the Albany Medical School, and an assistant attending physican at the Albany Medical Center Hospital. Dr. Greenwald gave very effective testimony before this committee last July on DES, and it is a pleasure to welcome him back here again today.

STATEMENT OF PETER GREENWALD, M.D., DIRECTOR, CANCER CONTROL BUREAU, NEW YORK STATE

Dr. GREENWALD. I am Peter Greenwald, M.D., a licensed physician in New York State, and Director of the Cancer Control Bureau, New York State Department of Health. I was invited to present our current data on diethylstilbestrol (DES) and human cancer, the pattern of practice in New York State with respect to DES as a morning after pill, and my opinion about its use for this purpose. In general I feel that while DES may be useful as a morning after pill, present data on effectiveness and, especially, on possible risks are inadequate.

In the July 20, 1972, hearings of this subcommittee, I described nine teenage girls who developed vaginal cancer after their mothers took DES or a similar drug during pregnancy. They were 15 to 19 years old at diagnosis. Six of these girls died of advanced disease.

A cause-and-effect relationship between therapeutic use of DES by mothers and vaginal cancers in their daughters was demonstrated by comparing drug usage in these mothers to mothers of other girls of the same age and place of birth, by birthdates of all nine patients occurring during peak clinical use of DES to prevent miscarriages, and by the rather uniform microscopic pattern of these tumors supporting the possibility of common cause. The observations were in keeping with independent investigations of others and are consistent with our biologic knowledge of DES and particularly with the fact that DES can be shown to produce cancer in a variety of animals.

"Cause-and-effect relationship" means that the DES is a necessary factor and the cancers will not develop without it. There are undoubtedly additional factors affecting susceptibility and resistance, which are yet to be uncovered.

Since the hearings of last July, we have obtained suggestive evidence that daughters are at risk only if their mothers start DES during the first three months of pregnancy, and that mothers whose children developed vaginal cancer received higher dosages than other mothers who received DES for the same purpose. This further supports a cause-and-effect relationship.

The same maternal drug association now has been demonstrated for clear-cell adenocarcinoma of the cervix as exists for vaginal cancer.

Senator KENNEDY. Let me see if I understand you correctly. On the basis of your research, you conclude that this drug has a direct causal relationship in two different types of cancer; is that correct?

Dr. GREENWALD. Cancer of two different sites that are anatomically next to each other.

Senator KENNEDY. So that in addition to vaginal cancer you also have clear-cell adenocarcinoma?

Dr. GREENWALD. Yes, a type of cancer of the cervix, in daughters born of mothers who have had DES.

Senator KENNEDY. And this is something different from what you mentioned to us last July, as I understand it?

Dr. GREENWALD. Yes. Actually across the country in the collaborative data that Herbst and his colleagues have been collecting I believe about a third of over a hundred patients have the cervix cancer rather than vaginal cancer.

In addition, we have studied extensively prenatal DES experience of mothers of boys and girls with many other types of cancer, and thus far have not found an association of these other tumors with maternal drug use.

In order to gather information about the pattern of use in New York State of DES as a morning-after pill, last week we surveyed 14 of the States' largest colleges and universities, 14 large hospitals—primarily those associated with medical schools, and 14 planned parenthood organizations, for a total of 42 institutions.

This survey may be biased toward those institutions most likely to use DES as a morning-after pill. Contact was made with knowledgeable respondents in student health services, directors of outpatient gynecology services, and directors of community planned-parenthood organizations. Results are shown in the appended table.

It can be seen that 12 of the 42 institutions now prescribe DES as a morning-after pill, and 11 others refer to prescribing physicians. Thus, about half of the institutions prescribe or refer to physicians who prescribe DES as a morning-after pill. Four institutions formerly used DES; two of these were influenced to stop as a result of the Food and Drug Administration circular on DES and vaginal cancer.

Some of the planned parenthood and other institutions have an administrative directive against DES use.

Senator KENNEDY. So, in other words, their directive—and I have a copy and will include it in the record—recommends against the use of DES?

Dr. GREENWALD. That is correct.

[The following was subsequently supplied for the record:]

MEMORANDUM

PLANNED PARENTHOOD-WORLD POPULATION
810 Seventh Avenue
New York, New.York 10019

TO: Executive Directors, Medical Directors, Chairmen, Medical Advisory Committees

FROM: National Medical Department DATE: November, 1971

SUBJECT: STATEMENT ON POSTCOITAL CONTRACEPTION

The National Medical Committee continued its review of the paper "Adenocarcinoma of the Vagina". You are aware that the paper has caused the FDA to review the labelling of diethylstilbestrol and related compounds. The labelling changes will be mailed to all physicians by the FDA as part of a "Dear Doctor" letter. In the meantime, the National Medical Committee was concerned about the use of diethylstilbestrol and related compounds as postcoital contraceptive agents. As a result of their deliberations, at the National Medical Committee meeting on November 17, 1971, the statement on postcoital contraception has been amended as follows: This statement supercedes Order #1653/370.

STATEMENT ON POSTCOITAL CONTRACEPTION

The technique of postcoital contraception, using particularly stilbestrol and ethinyl estradiol cannot be considered to be an approved method of contraception. A prime factor in this recommendation by the Medical Committee is the lack of FDA approval of such drugs for contraception. Planned Parenthood Affiliates should familiarize themselves with some of the available literature on the subject. We suggest the following references:

1. "Postcoital Oral Contraception", Morris and Van Wagenen, reprinted from the Proceedings of the Eighth International Conference of International Planned Parenthood Federation, Santiago, Chile, April 9-15, 1967.

2. "Postcoital Antifertility Agents and Their Teratogenic Effect", Morris. World Health Organization, Geneva, November 11-15, 1968.

3. "Postcoital Contraception with Diethylstilbestrol", Lucille K. Kuchera, Journal of the American Medical Association, October 25, 1971, Vol 218, #4, Pg. 562.

4. "Postcoital Contraception", C.W. Emmens, British Medical Bulletin, Vol. 26, #1, Pg. 45-51, January, 1970.

It is apparent that this could be a promising technique and deserves much more intensive research effort. Therefore, the National Medical Committee recommends that further efforts be made to test postcoital contraception using estrogens other than diethylstilbestrol.

By complying with the rather simple requirements of the FDA, various research protocols could be developed. The National Medical Committee would like to make itself available on request to assist with the development of adequate research protocols.

Senator KENNEDY. Do any of the organizations you refer to here use that drug?

Dr. GREENWALD. Yes, about half of the organizations use the drug, but among——

Senator KENNEDY. How many are Planned Parenthood?

Dr. GREENWALD. It is on the back sheet. Of the 14 planned parenthoods, two use the drug themselves, and five others refer to places who use it.

So in total, half of the 14 use it. Those are not the ones who told us they have a directive from above in the Planned Parenthood. The other seven were the ones that mentioned this directive.

Data on the number of women treated are fragmentary. Summing the estimates for each institution yields a minimal estimate of 450 women treated or referred by the 42 institutions in the past year. The highest frequency of use seems to be at colleges and universities. Doseages were generally 25 to 50 milligrams of DES per day for five days, and nausea was reported as a side effect of the drug.

We could not identify a single woman who, after taking DES, was known to become pregnant and have a child. Physicians using DES felt it was effective if administered correctly. I must emphasize, however, that frequently there is no followup of treated women, and we cannot be certain that no births resulted.

There is a definite cancer risk to daughters born of pregnancies where DES was taken. It seems likely that widespread use of DES as a morning after pill will result in some daughters born with this vaginal cancer risk, either because of an excessive time lapse between conception and DES prophylaxis, or because of other forms of treatment failure. Morning after pills with a better likelihood of safety perhaps can be developed.

Senator KENNEDY. We just heard some testimony from Dr. Wolfe about the statistics and the University of Michigan Medical Center, that people who were getting pregnant even with the use of it.

As I gather from what you are saying here, you are going to be able, based upon your derivatives and numbers that there will be women who will contract cancer. There will be casualties?

Dr. GREENWALD. We cannot say it absolutely, but I think it seems likely that some women will become pregnant, have daughters, and that some of those daughters may very well get vaginal or cervical cancer.

I am not sure that if it is used exactly as originally described that would happen, but I do not think it will always be used that way.

Senator KENNEDY. Yes.

Dr. GREENWALD. It is doubtful if five days of DES ingestion results in an increased danger of malignancy to the woman herself. On the other hand, prolonged use of DES has been implicated as a possible causative factor for uterus cancer, and estrogens increase the activity of breast cancer cells. DES as a morning after pill most certainly is not the contraceptive method of choice.

Several studies suggest that DES is effective as a morning after pill. In some cases, women may be prepared to interrupt their pregnancies if DES does not work. In my opinion, there have been insufficient comprehensive and controlled scientific studies of risks as well as effectiveness of DES as a morning after pill.

Available data in total, therefore, do not meet the high standards that we should be able to expect in this country before a drug is widely used for a designated purpose.

As a final point, I want to mention that there are medical situations in the treatment of cancer where DES is a useful drug and its benefits outweigh its risks.

Senator KENNEDY. We have heard earlier this morning that DES is being used as a morning after pill in a number of different university medical centers. We have heard also this morning, using your own figures, that about half of the institutions in New York that you have sampled have either been prescribing it themselves or referring young women to sources where they can obtain it.

You have also testified as to the casual relationship between the use of DES and the effect that it can have on female children of users.

What can we do to prevent this kind of thing from happening with other drugs?

Dr. GREENWALD. I think the first thing—this has happened quite a number of times in the past few decades with different drugs—we should do, rather than back into the widespread usage of a medication, is to make sure it is adequately studied.

I think there should be a responsibility here for well controlled. scientific study to find just what the efficacy is and just what the risks are. We have not had that.

I think we should avoid doing things that will encourage widespread use during this interim period.

I was a little concerned about whether or not the action of the FDA would actually encourage wider use rather than greater scientific study.

Senator KENNEDY. You have been able to, as a result of your studies, show that it has caused two different types of cancer. What is the possibility that it causes other kinds of cancer? I understand it has an association with cancer of the breast and uterine cancer.

Dr. GREENWALD. I cannot give you a percentage figure because we really just do not have that. We know that in animals DES given to the animals themselves, mainly rats, mice and hamsters, can cause cancer of many different types of organs.

It can cause cancer of the glands like the pituitary and the adrenal, the breast and prostate, and the urogenital system, the kidney, the bladder, ovaries, and other organs.

So there are a wide number of animals that get cancer, but under different laboratory manipulations.

Now, in humans we know that young women before menopause who have breast cancer and are treated with DES can respond quite differently. Some of them will have an aggravation of their disease. It seems to develop faster, so there is a possible risk of estrogens, not only DES, aggravating breast cancer.

This is further supported by knowledge that removing the ovaries decreases estrogens and lowers breast cancer risk. So all we have is some circumstantial evidence that it is conceivable there would be other risks, but it is not proven, and it is also not proven how DES varies from normal estrogens in the body.

There are just a lot of open questions.

Senator KENNEDY. What was your reaction to the suggestion yesterday by Dr. Edwards that DES would soon be permitted in emergency situations like rape?

Dr. GREENWALD. My reaction was that every woman who comes in, most of them, and says she wants it, will consider it to be an emergency situation to her, so actually this was an encouragement of widespread use.

I think personally that it is unfortunate to take an official action that encourages widespread use when what we should be doing is taking official action to see that it is well investigated, and that we have looked at all alternatives.

Senator KENNEDY. If you had been Commissioner would you advocate that step?

Dr. GREENWALD. Yes.

Senator KENNEDY. Which one? I am not talking about followup. I am talking about the use.

Dr. GREENWALD. Oh, I would not advocate the action that the Food and Drug Administration took. I would advocate adequate studies with followup perhaps through contracts and some thorough consideration of this.

I do not think I would take a step at this point to block DES, because it has other uses, and I think we should find out the risks at this point, but this can be done rather quickly with well defined investigations.

I think perhaps the steps I would take would be more along the lines of warning what the known risks are, rather than encouragement of use.

Senator KENNEDY. Is it your feeling that the steps taken by the Food and Drug Administration to permit its use in emergency situations would mean there would be more widespread use?

Dr. GREENWALD. Yes, I would think it would be interpreted as an okay to go ahead and use it whenever you want.

Senator KENNEDY. And that is good or bad?

Dr. GREENWALD. That is bad.

Senator KENNEDY. Let me pose a related question with regard to the prescription of a drug for an unapproved use. A doctor can prescribe on the basis of his own judgment for an unapproved usage; as a researcher do you think we ought to let that practice continue?

Dr. GREENWALD. Yes. I think within the present system of medical care that it is not really possible to affect that too directly. If drugs can be prescribed, I just do not see a practical way to prevent it, prescribing it in somewhat different manner, so it is a matter that just rests with the educational processes and peer review which I agree are somewhat inadequate, but I do not see a practical way to control that.

Senator KENNEDY. And what are we going to do about it? You told us before if FDA approved DES for emergency use there will be a wider use of this type of drug, virtually a green light toward it being used in many of these medical centers.

You have some serious reservations, concerns, and then you come to the conclusion that doctors ought to be able to prescribe independently.

Dr. Greenwald. Yes, I still think there are some things that can be done. I think the first really—maybe I am biased toward research—there are certain things that we just have to know, and they are not so difficult to find out.

We have the technology. It is just a matter of information gathering. We have all sorts of computer abilities and other types of abilities to get this information quickly so we just need a mechanism for a rapid evaluation of questions such as the question of DES as the morning after pill, and methods for dispensing this information.

I think in a concentrated study you could find out within six months at that point you might want to take some direct action to prevent the use for a purpose or not prevent it, but I do not think we have enough facts at this point.

Senator Kennedy. Do I gather from what you said that it ought to be very much controlled in terms of collecting data, using experimental drugs only in controlled settings?

Dr. Greenwald. Yes. That is the time when we need very tight control of who is getting it and what are its affects, and some good scientific study designs.

Senator Kennedy. Thank you very much.

Our next witness will be taken out of order. Dr. Donald Harrington has a plane to catch. He came all the way from California. His testimony has been enormously valuable when he testified before the committee previously.

He is president of the San Joaquin Foundation for Medical Care in Stockton, California. He is accompanied by Dr. Robert Talley, the association medical director of the San Joaquin Foundation.

We want to welcome you very much. We think that your experience in San Joaquin can be terribly important and useful and helpful to us in this set of hearings.

I want to express very much our appreciation for your taking the time to join us.

STATEMENT OF DONALD HARRINGTON, M.D., MEDICAL DIRECTOR, ACCOMPANIED BY ROBERT TALLEY, M.D., ASSOCIATE MEDICAL DIRECTOR, SAN JOAQUIN FOUNDATION FOR MEDICAL CARE, STOCKTON, CALIF.

Dr. Harrington. Senator Kennedy and members of the Senate Health Subcommittee, I am Donald C. Harrington, M.D., a practicing obstetrician and gynecologist. I am also medical director of the San Joaquin County Foundation for Medical Care, and president of the American Association of Foundations for Medical Care.

I also serve on the Peer Review committee of the American College of Obstetricians and Gynecologists.

With me is Dr. Robert Talley, a practicing gastroenterologist and associate medical director for the San Joaquin County in charge of the medical care program's drug review. Dr. Talley serves on the Community Service Committee of the American College of Physicians, and represents the College on the Board of Trustees of the Commission on Professional Hospital Activities.

Our presentation will include, one, a brief background for the study; two, the body of the testimony by Dr. Talley; and, three, a brief summation and description of "model treatment".

The San Joaquin Foundation has been reviewing all providers except institutions since the inception of the Medicaid program. It has functioned as an HMO for physicians' services over the past five years, and for pharmacy services for the past three.

As an HMO it has administered the program, done peer review, gathered data and documentation that has been essential.

Our peer review program is at present basically a manual review process with computer backup. By these methods we have been able to improve quality and decrease cost.

These matters were presented in much more detail to the committee last year.

Today our emphasis is on the extremely complicated matter of drug review. This cannot be done in a vacuum, and must perforce relate to other services required by the patient, particularly office visits and injectibles and to the diagnoses being given.

To give you an understanding as to the magnitude of the problem, the following figures are relevant. In January of 1973 for a caseload of some 42,000 Medicaid recipients, the following claims were received:

Hospital inpatient	1, 000
Hospital outpatient	3, 000
Other providers	2, 400
Physician	14, 150
Pharmacy	34, 500

The problems of manual drug review is obvious, and the need for a total computerization is self-evident.

Dr. Talley will now present the body of our testimony.

Dr. TALLEY. In the current national emphasis on the upgrading of the quality of medicine, the San Joaquin Foundation for Medical Care has had a unique opportunity to study drug prescribing patterns as one facet of improving both quality and cost effectiveness of health care. The need for research and appropriate controls in this area is readily apparent from data showing that the number of prescriptions dispensed is rising at a rate of 6.6 percent per year (1) and the average practicing physician prescribes some pharmacological agent for 75 percent of the patients he treats (2). Thus, our profession can justifiably be concerned with possible problems of drug dependency, adverse drug reactions and costs.

Senator KENNEDY. Clearly you do not believe there is adequate control and regulation now outside the San Joaquin Foundation.

Dr. TALLEY. Correct. There are some other foundations that have the same program in effect.

It is in light of such considerations that the San Joaquin Foundation for Medical Care has applied peer review techniques to monitor drug prescribing through a multi-disciplinary approach using the knowledge and skills of both physicians and pharmacists. It is the purpose of this testimony to report an overview of our program.

The four-county area served by the San Joaquin Foundation for Medical Care (San Joaquin, Tuolumne, Calaveras, and Amador) includes 385 physicians, 112 pharmacies, and a population of 338,000 patients. Under our foundation program, pharmacies filling prescriptions for medicaid patients are reimbursed through a subcontractor, Paid Prescriptions. As a part of their claims processing, Paid Prescriptions have developed a variety of reports which permit detailed review of drugs prescribed and dispensed.

Thus, we now have the means of analyzing drug information which has heretofore remained in physicians' possession or pharmacists' records, with no practical means of analyzing it on a mass scale.

Senator KENNEDY. Let me ask you. Is it your impression that your system could be adapted as a national system?

Dr. TALLEY. I think it could.

As a result, we have been able to study prescribing patterns of outpatient care for the medicaid population in our area, and to note the impact of our peer review.

Peer review is performed by the Drug Utilization Review Committee (DURC), whose task is to analyze reports and identify problem areas. The Drug Utilization Review Committee is a joint endeavor by physicians and pharmacists. The ability to supply a knowledgeable multidisciplinary team with a powerful set of information has provided the San Joaquin Foundation for Medical Care with the capability of identifying drug utilization by patients, physicians, and pharmacists. It is our experience that drug abuse is encountered in all three areas.

Senator KENNEDY. Is it your impression that there is no national system doing what you are doing?

Dr. TALLEY. I know of no national program in the Nation similar to this one.

Senator KENNEDY. Thank you.

Dr. TALLEY. Our multidisciplinary system is based on three separate but interrelated ideas: documentation, communication, and education. In our experience, documentation is solely an administrative function; communication utilizes a combination of administrative and professional techniques while education, when it occurs, is motivated by the force of peer persuasion.

Let us state unequivocally our belief that peer review cannot occur without adequate documentation, and that the most sophisticated and elaborate administrative system is of little value if it is not backed by solid professional participation and support.

Every 2 weeks, while processing the drug claims for payment, the computer automatically furnishes the following reports:

1. Duplicate payment report.
2. Refill control report.
3. Appropriate quantity report.

4a. Physician, pharmacist, and drug profiles listed by therapeutic class.

b. Area drug profile listed by therapeutic class.

5. Exceptional patient report.

The following are brief descriptions of the types of reports provided to the Drug Utilization Review Committee:

The duplicate claim report lists by pharmacy order, any claim for a prescription for the same drug prescribed by the same physician, dispensed by the same pharmacist, on the same date, for the same patient. The reviewers challenge the pharmacist by furnishing him copies of the original prescription, the date it was paid, the check number, and a copy of his duplicate claim.

If the pharmacist cannot validate the duplicate claim, payment is denied. If the duplicate claim is due to a billing error or accidental loss of the medication by the patient, the duplicate claim is given an over-ride code and processed for payment.

When this program was begun, we discovered that 10.4 percent of claims were duplicates.

Senator KENNEDY. What do you mean by duplicates?

Dr. TALLEY. Patient prescription duplicates. The pharmacy makes a claim for remuneration for it, and if the mechanism is not fast enough, as they are in many systems that pay for this third party type thing, the pharmacist who is working on a different capital basis resubmits a billing, and we found that 10.4 percent the first month were duplicates.

After 7 months it was down to .4 of 1 percent, which is a hundredfold decrease.

Senator KENNEDY. What happens? Did you find out what percent of those were paid?

Dr. TALLEY. Under our program none of those. I do not know what has happened before. I have no way of knowing. This is part of the third party pay program. If they do not have this kind of check, I would imagine they are paying it.

After the review program had been in operation for seven months, the duplication rate was down to 1.4 per cent. If the San Joaquin experience is typical, the national implication for this finding is very substantial.

Senator KENNEDY. You are moving through rapidly. There is a lot of meat in this testimony, as you well understand we are indeed appreciative of it. We want to hear it all.

You say, "if the San Joaquin experience is typical, the national implications for this finding is very substantial."

Would you elaborate a little bit on that?

Dr. TALLEY. As you well know, I wrote another paper that was given in Sea Island, Georgia, and this is cut down from 45 minutes to 10, so I cannot tell you everything I did before.

Senator KENNEDY. We are going to put that in the record.

Dr. TALLEY. Fine.

[The following was subsequently supplied for the record:]

DRUG UTILIZATION AND PEER REVIEW
IN SAN JOAQUIN

by

Robert B. Talley, M.D., F.A.C.P.

Marc F. Laventurier, B.S. Pharm., F.A.C.A.

Robert B. Talley is the Associate Medical Director of the San Joaquin Foundation for Medical Care and in the practice of Internal Medicine and Gastroenterology in Stockton, California.

Marc Laventurier is Vice President of Professional Services for PAID Prescriptions, San Mateo, California, and Secretary of the San Joaquin Drug Utilization Review Committee.

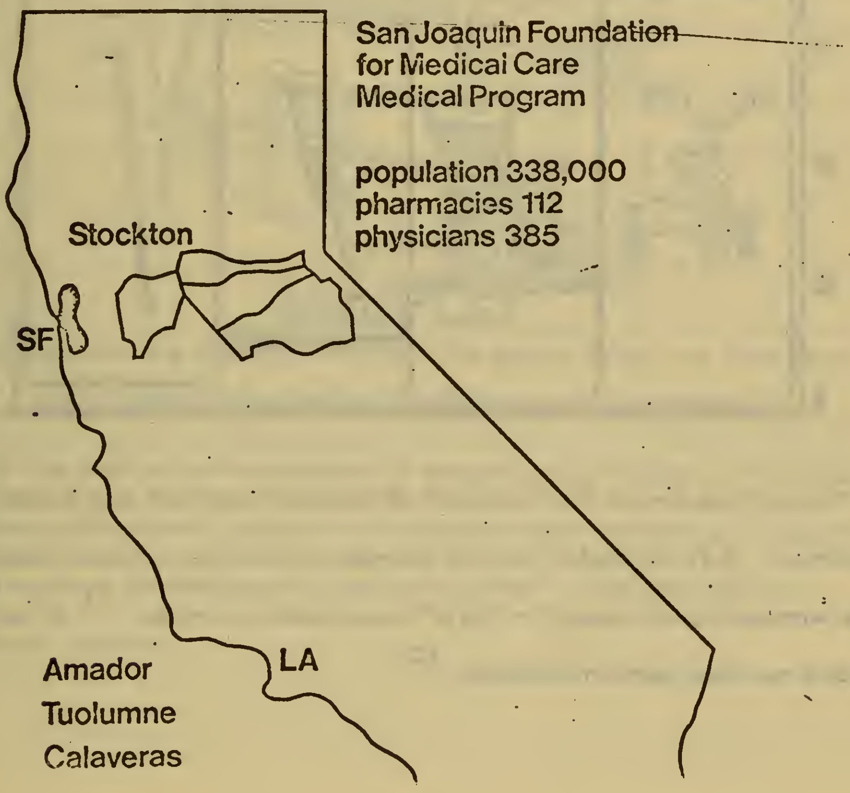
Presented before the American Association of Foundations for Medical Care in Sea Island, Georgia, on August 28, 1972.

Requests for reprints should be addressed to San Joaquin Foundation for Medical Care, Stockton, California.

The delivery of health care has become the primary objective for the health professions in the 1970's; to achieve this objective we must assume the responsibility to deliver quality care at an equitable and predictable cost. The participation of health professionals in public assistance programs has given them an opportunity to affect the development of multidisciplinary systems designed to improve patient care at each point of service. We currently participate in such a multidisciplinary program, and we believe that we can demonstrate its effectiveness as a peer review organization.

The recent shift in health care toward more comprehensive programs of coverage has forced health professionals to re-evaluate their standards of practice within each locality; in essence each well organized system of health care delivery creates its own profile of utilization whether it involves physician, pharmacy, or hospital services. By studying these profiles and documenting unusual cases, professionals can engage in an activity which is designed to improve the health of the community. This process is called "Peer Review" and might be defined as the study of data by health professionals who investigate utilization patterns and communicate those results and recommendations to their peers with the view of sharing valuable information about the health status of the community or individual patients.

Since 1968 the San Joaquin Foundation for Medical Care has administered the State Medicaid program for medical care for Title XIX patients. The region covered by the San Joaquin Foundation for Medical Care consists of four counties in Northern California and can be considered a microcosm of many regions in the United States. It consists of three rural mountain counties and an urban center, Stockton, in the largely agricultural county of San Joaquin. The total population of the four counties is over 338,000. The census of practicing physicians is 385 and the number of pharmacies 112. The Medi-Cal patient population varies in number from 48,000 to 51,000.



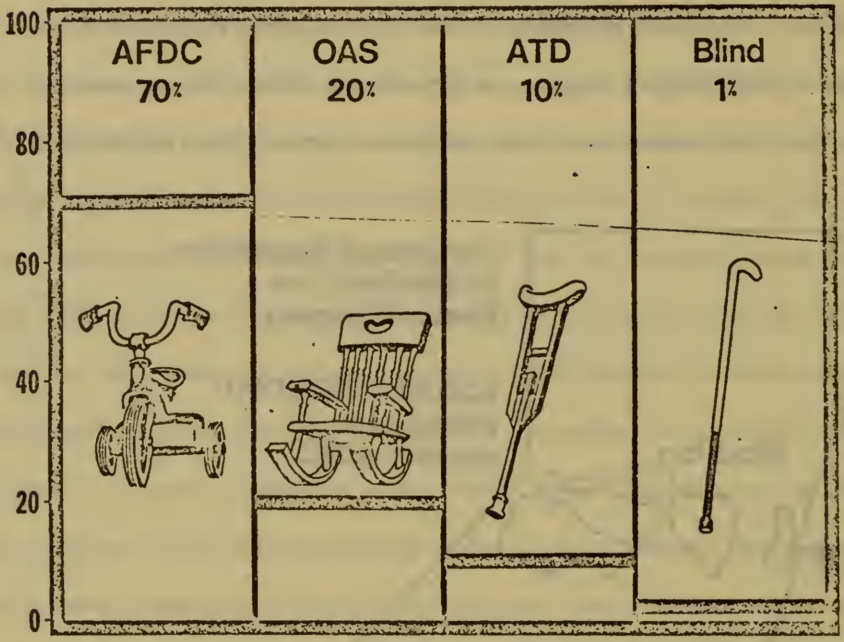
The distribution of patients in the various aid categories is approximately as follows:

Aid to Families with Dependent Children - 69.5%

Old Age Security - 19.5%

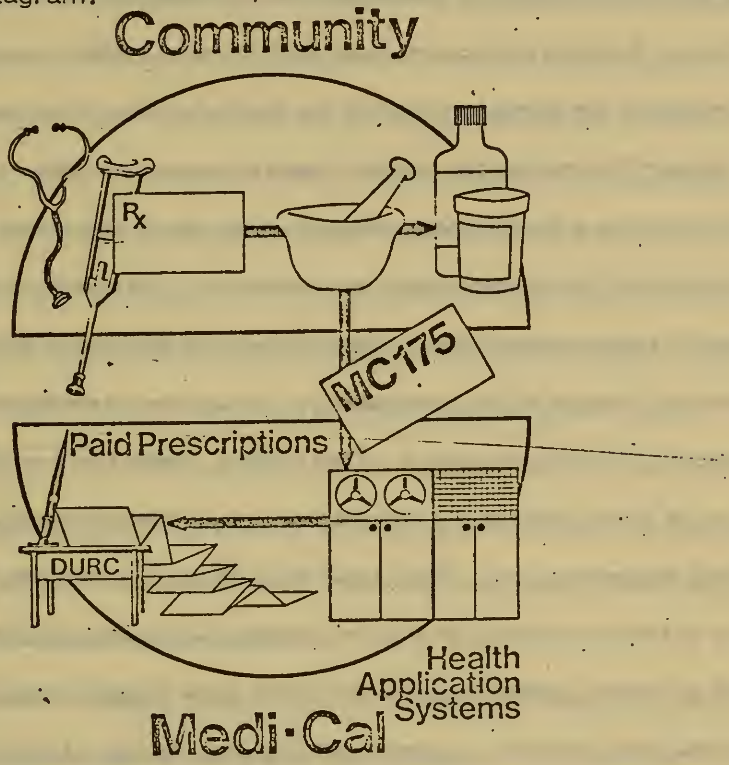
Aid to the Totally Disabled - 10.2%

Aid to the Blind - 0.8%



Today drugs are an intrinsic part of medical treatment and disease management. It is estimated that the average practicing physician prescribes some pharmacological agent for 75% of the patients he treats. (1) In our program 84% received some medication. (2)

When a physician in the community determines that a medication is indicated, the traditional pattern of drug distribution occurs as illustrated in the top of the diagram.



The physician writes a prescription which the patient takes to a local pharmacist who dispenses the drug, and the patient takes the medication home. Up to now, it has been almost impossible to capture accurate data on the patterns of drug use by ambulatory patients who receive treatment from private practitioners because the information lies buried either in the physicians' or pharmacists' records.

In our administration of this model peer review drug program the data regarding this transaction is listed in a form suitable for capture by electronic data processing techniques on the drug claim (MC-175). The pharmacist submits his accumulated MC-175's to PAID Prescriptions who subcontracted the administration of the Medi-Cal Drug Program from the San Joaquin Foundation for Medical Care in August of 1970. PAID is required to act as a fiscal intermediary and pay the drug claims to the pharmacists as well as to implement the formation of this multidisciplinary drug utilization review committee. Peer review in pharmacy is difficult to administer because of the customary way drugs are distributed in a community. For the protection of the patient, there has been an historical division of labor between the physician's prescribing function and the pharmacist's dispensing role. This separation of service has offered us the chance to test the validity of a premise that given an opportunity two different groups of health professionals could retain their independence yet participate in a model drug delivery system involving peer review within the Foundation's structure.

PAID has retained a computer organization, Health Application Systems, to process drug claims. While processing the drug claims for payment, all the pertinent information about the prescription and the patient is tabulated and a series of reports is generated in a form suitable for review by the appropriate professional committee, in this instance the Drug Utilization Review Committee or D.U.R.C. This system gave the San Joaquin Foundation for Medical Care the capability of developing a unique drug review mechanism which is used to identify drug abuses by patients, physicians, or pharmacists.

Our multidisciplinary system is based on three separate but interrelated ideas: documentation, communication, and education. In our experience documentation is solely an administrative function; communication utilizes a combination of administrative and professional techniques while education, when it occurs, is motivated by the force of peer persuasion. Let us state unequivocally our belief that peer review cannot occur without adequate documentation and that the most sophisticated and elaborate administrative system is of little value if it is not backed by solid professional participation and support. Any efficient drug review system must routinely and automatically furnish accurate reports that give complete documentation so peer review can occur and concern itself with the inter- and intra-professional communication and educational components of the process.

Every two weeks, while processing the drug claims for payment, the computer automatically furnishes the following reports:

1. A duplicate payment report
2. A refill control report
3. An appropriate quantity report
4. Physician, pharmacist, and drug profiles listed by therapeutic class
5. An area drug profile listed by therapeutic class
6. An exceptional patient report

These reports are subjected to professional review by staff pharmacists.

The duplicate claim report lists by pharmacy order any claim for a prescription for the same drug prescribed by the same physician dispensed by the same pharmacist on the same date for the same patient. The reviewers challenge the pharmacist by furnishing him copies of the original prescription, the date it was paid, and the check number as well as a copy of his duplicate claim. If the pharmacist cannot validate the duplicate claim, payment is denied. For example, if the duplicate claim is due to a billing error or accidental loss of the medication by the patient, the duplicate claim is given an over-ride code and processed for payment. When this program was initially instituted, this review saved the program approximately 10%; since then the rate of duplicate claims has decreased to less than 0.1%.

PAID PRESCRIPTIONS
RUN DATE: APRIL 14, 1972

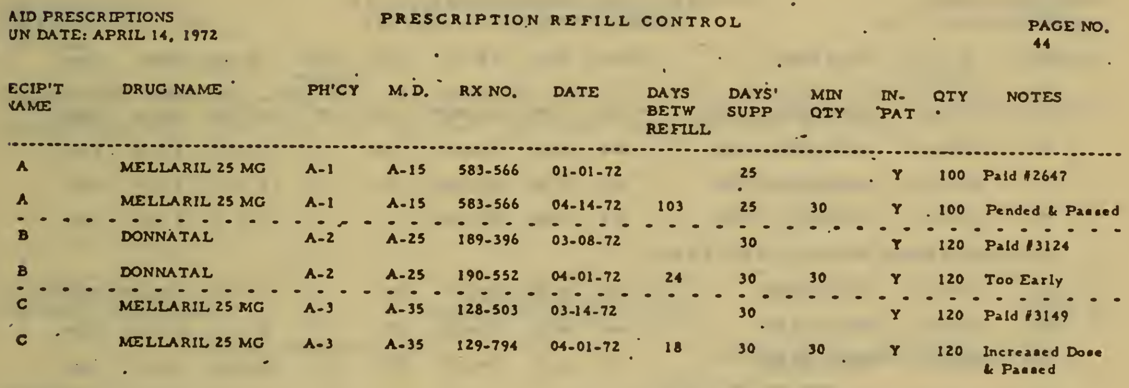
DUPLICATE PAYMENTS

PAGE NO.
3

RECIP'T NAME	DRUG NAME	PH'CY	M.D.	RX NO.	QTY	DAYS' SUPP	BILLED	PAID	CODE
A	LANOXIN 0.25 MG	A-1	A-15	111-748	30	30	$2.60	$2.37	DUPLICATE
A	LANOXIN 0.25 MG	A-1	A-15	111-748	30	30	$2.60	$2.37	DUPLICATE
B	TETRACYCLINE 250 MG	A-2	A-25	100-730	36	9	$3.70	$3.50	PAID #7425
B	TETRACYCLINE 250 MG	A-2	A-25	100-730	36	9	$3.70	$3.30	DUPE-DENIED

Duplicate = same Recipient, Date, Pharmacy, M.D., Drug.

The refill control report is designed to check the elapsed time between refills according to the days' supply of medication. It also differentiates between in-patients and ambulatory patients as there are some quantity formulary restrictions imposed on patients in nursing homes. The reviewer challenges any prescription which in his judgment is refilled too soon according to the physician's directions. If the pharmacist can document an authorized dosage change or any other valid reason, the claim is passed for payment; otherwise payment is automatically denied.



AID PRESCRIPTIONS
UN DATE: APRIL 14, 1972

PRESCRIPTION REFILL CONTROL

PAGE NO.
44

ECIP'T NAME	DRUG NAME	PH'CY	M.D.	RX NO.	DATE	DAYS BETW REFILL	DAYS' SUPP	MIN QTY	IN-PAT	QTY	NOTES
A	MELLARIL 25 MG	A-1	A-15	583-566	01-01-72		25		Y	100	Paid #2647
A	MELLARIL 25 MG	A-1	A-15	583-566	04-14-72	103	25	30	Y	100	Pended & Passed
B	DONNATAL	A-2	A-25	189-396	03-08-72		30		Y	120	Paid #3124
B	DONNATAL	A-2	A-25	190-552	04-01-72	24	30	30	Y	120	Too Early
C	MELLARIL 25 MG	A-3	A-35	128-503	03-14-72		30		Y	120	Paid #3149
C	MELLARIL 25 MG	A-3	A-35	129-794	04-01-72	18	30	30	Y	120	Increased Dose & Passed

The inappropriate quantity report lists various drugs which fall outside certain criteria which were set as being either too large or too small quantities based on current pharmacological knowledge. For example, if we set an arbitrary low figure of 39 doses per Rx for Gantrisin and a high figure of 101 doses, the professional reviewer has an opportunity to examine all prescriptions which fall outside the accepted range (39 to 1 and 101 to infinity). This report is a valuable tool to reveal instances of prescription splitting, too frequent renewals of chronic medication, short counts, billings for prescriptions not dispensed, and "loading" patients prior to a program change.

PAID PRESCRIPTIONS
RUN DATE: APRIL 14, 1972

RX CLAIMS EXCEPTION REPORT
INAPPROPRIATE QUANTITIES

PAGE NOS.
3, 5, 7, 42
(SUMMARY)

RECIPIENT	DATE OF SERVICE	DRUG NAME	PH'CY	M. D.	RX NO.	QTY	DAYS' SUPPLY	BILLED	PAID	CODE
A	04-06-72	GANTRISIN 0.5 GM	A-1	A-15	456-289	360	90	$11.85	$10.05	HIGH
B	04-06-72	GANTRISIN 0.5 GM	A-2	A-25	134-297	36	4	$ 3.25	$ 3.05	LOW
C	04-06-72	GANTRISIN 0.5 GM	A-3	A-35	974-995	180	60	$ 4.10	$ 4.10	HIGH
D	04-06-72	SULFISOX. 0.5 GM	A-4	A-45	200-223	32	4	$ 3.15	$ 3.00	LOW
Note: Average number of doses per RX = 69 @ $3.93										
E	04-06-72	PEN G 250 MG	A-5	A-55	131-377	100	8	$ 4.80	$ 4.80	HIGH
F-1	04-06-72	PEN G 250 MG	A-6	A-65	114-224	200	10	$ 5.70	$ 5.70	HIGH
F-2	04-06-72	PEN G 250 MG	A-6	A-65	114-225	200	10	$ 5.70	$ 5.70	HIGH
Note: Average number of doses per RX = 28 @ $2.84										
G	04-06-72	TETRACYCLINE 250 MG	A-7	A-75	336-394	10	3	$ 2.60	$ 2.60	LOW
H	04-06-72	TETRACYCLINE 250 MG	A-8	A-85	131-158	8	2	$ 2.70	$ 2.05	LOW
I	04-06-72	TETRACYCLINE 250 MG	A-9	A-95	138-346	63	7	$ 3.15	$ 3.15	HIGH
Note: Average number of doses per RX • 28 @ $3.23										
J	04-06-72	DIGOXIN 0.25 MG	A-10	A-105	589-108	8	30	$ 2.40	$ 1.85	LOW

The therapeutic class profile is one of the most useful monitors of current drug use. All drugs dispensed in the San Joaquin program are recorded according to 99 therapeutic categories and by individual drug for each pharmacy, physician, and patient on a bi-monthly basis. These profiles of drug utilization for each therapeutic class are a valuable measurement of drug use and an indicator of possible inappropriate prescribing, dispensing, and drug taking. It has been found that given a long enough period of time and enough accumulated data, on the average, each pharmacy will have a similar percentage activity in each therapeutic class of drug. This should be self-evident since patients are all subject to similar diseases treated by similar therapeutic procedures dictated by local custom. We monitor the therapeutic

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PAID PRESCRIPTIONS                      THERAPEUTIC CLASS PROFILE                              PAGE NO.
RUN DATE: APRIL 14, 1972                     DRUG ANALYSIS                                     00044

THERAPEUTIC CLASSES   01    04    07    11    14    16    21    22    40    46    47    48    74    79    87
-----------------------------------------------------------------------------------------------------------
PERCENT OF RX/TCP    2.40  2.50  6.40  1.10  4.80  5.30  6.20  4.30  7.50  5.80  2.00  1.20  2.60  7.90  1.20
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PAID PRESCRIPTIONS
RUN DATE: APRIL 14, 1972                PHYSICIAN PROFILE                                        PAGE NO.
                                    TYPE:"PHYSICIAN ABUSE"                                       0052
                   PHYSICIAN NAME: K. W. L.
                                                          LICENSE NO. 000A1000   SPECIALTY: G. P.

THERAPEUTIC CLASSES  01    04    07    11    14    16     21    22  | 40     46     47  | 48    74    79    87
------------------------------------------------------------------------------------------------------------
PERCENT OF RX/TCP   2.10  2.40  4.50  .60   4.20  12.00  2.00  7.40 | 16.50  15.00  4.20 | .90   .50   7.30  .10
                                                                    |                   |
                            COMPARE THIS PHYSICIAN'S PROFILE        |                   |
                          TO THERAPEUTIC CLASS PROFILE SUMMARY:     |                   |
                                                                    |                   |
THERAPEUTIC CLASSES  01    04    07    11    14    16     21    22  | 40     46     47  | 48    74    79    87
------------------------------------------------------------------------------------------------------------
PERCENT OF RX/TCP   2.40  2.50  6.40  1.10  4.80  5.30   6.20  4.30 | 7.50   5.80   2.00 | 1.20  2.60  7.90  1.20
```

class profile (TCP) for each physician and pharmacy compared to the area TCP. Any gross deviations from the area TCP offers the reviewers an opportunity to evaluate individual practices and respond where indicated.

PAID PRESCRIPTIONS
RUN DATE: APRIL 14, 1972

PHYSICIAN PROFILE
TYPE: "PHYSICIAN ABUSE"

PAGE NO.
00045

PHYSICIAN NAME: K. W. L.

LICENSE NO. 000A1000 SPECIALTY: G. P.

	CURRENT MARCH TO APRIL 1972					YEAR TO DATE OCTOBER 1971 TO APRIL 1972				
DESCRIPTION OF DRUG	NO. OF CASES	NO. OF RX'S	AMT PAID	AVER QTY	AVER AMT	NO. OF CASES	NO. OF RX'S	AMT PAID	AVER QTY	AVER AMT
40 **NARCOTIC ANALGESICS**										
CODASA 30 MG	3	3	$ 11.40	35	$3.80	6	6	$ 22	31	$3.61
EMPIRIN #2	0	0	$ .00	0	$ .00	3	3	$ 10	71	$3.40
ASA & COD 15 MG	4	4	$ 12.60	48	$3.15	20	22	$ 72	44	$3.27
APC WITH COD 30 MG	59	60	$291.10	76	$4.85	331	590	$2,762	61	$4.68
ANAGESE I GR	4	4	$ 32.70	88	$8.17	19	38	$ 332	86	$8.74
CODEINE SULF. 15 MG	0	0	$ .00	0	$ .00	1	1	$ 2	6	$2.45
CODEINE PHOS. 30 MG	0	0	$ .00	0	$ .00	1	1	$ 3	24	$3.15
PERCODAN FULL S	2	2	$ 7.40	25	$3.70	9	20	$ 80	27	$4.00
ALL NARCOTIC ANALGESIC		73	$355.20		$4.86		681	$3,284		$4.82

ID PRESCRIPTIONS
N DATE: APRIL 14, 1972

PHYSICIAN PROFILE
TYPE: "PHYSICIAN ABUSE"

PAGE NO.
0046

PHYSICIAN NAME: K. W. L.

LICENSE NO. 000A1000 SPECIALTY: G. P.

DESCRIPTION OF DRUG	CURRENT MARCH TO APRIL					YEAR TO DATE OCTOBER 1971 TO APRIL 1972				
	NO. OF CASES	NO. OF RX'S	AMT PAID	AVER QTY	AVER AMT	NO. OF CASES	NO. OF RX'S	AMT PAID	AVER QTY	AVER AMT
SEDATIVE BARBS										
UTICAPS 15 MG	0	0	$ .00	0	$ .00	1	~~2~~	~~$ 10.~~	120	$4.95
UTICAPS 30 MG	1	1	$ 5.25	100	$5.25	13	21	$ 96.	101	$4.55
UTICAPS 50 MG	2	2	$11.05	110	$5.52	11	17	$ 88.	103	$5.14
EMBUTAL CAPS 100 MG	10	10	$24.90	30	$2.49	87	154	$427.	32	$2.77
HENOBARB 15 MG	0	0	$ .00	0	$ .00	3	13	$ 32.	96	$2.46
HENOBARB 30 MG	17	17	$43.30	114	$2.54	136	213	$563.	104	$2.64
HENOBARB 60 MG	4	4	$10.70	100	$2.67	12	19	$ 51.	97	$2.69
HENOBARB 100 MG	0	0	$ .00	0	$ .00	1	4	$ 10.	30	$2.51
HENOBARB LIQ 20 MG 5C	0	0	$ .00	0	$ .00	5	[illegible]	$ 17.	108	$[illegible].45
CONAL 50 MG	1	1	$ 2.75	30	$2.75	1	2	$ 6.	30	$2.75
CONAL 100 MG	11	11	$29.85	30	$2.71	90	158	$441.	30	$2.78
CONAL 3 GR	0	0	$ .00	0	$ .00	1	1	$ 3.	30	$2.85
UINAL 100 MG	0	0	$ .00	0	$ .00	1	1	$ 3.	24	$2.90
UINAL 200 MG	1	1	$ 3.35	30	$3.35	6	11	$ 35.	28	$3.14
CETYLCARBROMAL SE	0	0	$ .00	0	$ .00	1	1	$ 7.	100	$6.80
LL SEDATIVE BARBS		47	$131.15		$2.79		622	$1,782		$2.86

The exceptional patient report is an automatic claim review mechanism which furnishes examples of possible abuses which might be patient-, pharmacy-, drug-, or physician-oriented. An individual patient profile is furnished automatically if the drug utilization falls within certain parameters. Any patient who receives twelve or more prescriptions, or over $30.00 in prescriptions in a 30-day period, any patient who receives the same drug from two pharmacists on the same date, any patient who receives services from four or more pharmacists in a 30-day period, and any patient who receives more than four prescriptions in one therapeutic category will appear on this exceptional patient profile. The exceptional patient profiles are furnished to the Drug Utilization Review Committee members for review and they decide if they are legitimate profiles of patients requiring much pharmaceutical support or if they are indications of patient-oriented abuses of recipients shopping for physician and pharmacist services to procure desired drugs. They also check for physician-oriented abuses which usually involve poor control of therapy through the prescribing of too many drugs in the same therapeutic category, drugs which interact, or too many drugs for too large a cost. The pharmacist-oriented abuses usually consist of duplicate billings and too frequent renewals for small or large quantities without proper authorizations.

PAID PRESCRIPTIONS
RUN DATE: APRIL 14, 1972

PATIENT PROFILE
TYPE: "PATIENT ABUSE"

PAGE NO.
2704

PATIENT NO. 00039 NAME: THOMAS S.

PRICE SHOPPER 40

THERAPEUTIC CLASS	DATE OF SERVICE	DRUG & STRENGTH	PH'CY	M.D.	IN PATIENT	RX NO.	QUANTITY	DAYS' SUPPLY
A IN JAIL >	JAN 26-72	CONDOMS	B	B	NO	66-684	144	30
A	APR 7-72	CONDOMS	B	B	NO	75-038	144	30
A	MAY 4-72	CONDOMS	B	B	NO	75-729	144	30
46	JAN 4-72	NEMBUTAL 100 MG	A	A	NO	72-242	15	15
46	JAN 17-72	NEMBUTAL 100 MG	D	A	NO	45-636	30	20
46	JAN 31-72	NEMBUTAL 100 MG	A	A	NO	72-742	30	15
46 IN JAIL >	FEB 8-72	NEMBUTAL 100 MG	D	G	NO	47-198	30	30
46	APR 7-72	NEMBUTAL 100 MG	A	A	NO	75-036	30	30
46	APR 28-72	NEMBUTAL 100 MG	A	A	NO	75-549	15	15
46	MAY 11-72	NEMBUTAL 100 MG	A	A	NO	75-924	30	30
46	MAY 25-72	NEMBUTAL 100 MG	A	A	NO	76-250	30	15

PAID PRESCRIPTIONS
RUN DATE: APRIL 14, 1972

PATIENT PROFILE
TYPE: "PATIENT ABUSE"

PAGE NO.
2705

PATIENT NO. 00039 NAME: THOMAS S.

PRICE SHOPPER 40

THERAPEUTIC CLASS	DATE OF SERVICE	DRUG & STRENGTH	PH'CY	M.D.	IN PATIENT	RX NO.	QUANTITY	DAYS' SUPPLY
40	JAN 1-72	EMPIRIN #4	C	C	NO	95-045	100	30
40	JAN 10-72	EMPIRIN #3	B	B	NO	72-667	50	15
40	JAN 17-72	PERCODAN (FULL)	D	B	NO	26-570	30	15
40	JAN 18-72	MEDAPIN 50 MG	B	B	NO	72-910	15	5
40	JAN 26-72	MEPERIDINE 50 MG	B	B	NO	73-079	20	4
40	FEB 1-72	EMPIRIN #3	D	D	NO	61-020	30	30
40 IN JAIL >	FEB 7-72	DEMEROL 50 MG	B	B	NO	73-423	30	7
40	APR 7-72	EMPIRIN #3	B	B	NO	75-034	30	15
40	APR 7-72	EMPIRIN #4	B	B	NO	75-035	30	15
40	APR 19-72	EMPIRIN #3	B	B	NO	75-322	40	15
40	APR 25-72	EMPIRIN #4	C	E	NO	4-700	50	16
40	APR 29-72	EMPIRIN #3	D	B	NO	52-507	30	4
40	MAY 4-72	EMPIRIN #3	B	B	NO	75-728	36	18
40	MAY 8-72	EMPIRIN #3	C	E	NO	5-953	40	10
40	MAY 11-72	EMPIRIN #3	B	B	NO	75-922	30	15
40	MAY 11-72	EMPIRIN #4	B	B	NO	75-923	30	15
40	MAY 15-72	EMPIRIN #4	D	B	NO	53-519	15	5
40	MAY 18-72	EMPIRIN #4	C	B	NO	6-891	30	15
40	MAY 25-72	EMPIRIN #4	B	B	NO	76-252	30	15
40	JUN 1-72	EMPIRIN #3	B	F	NO	76-429 SP	50	25
40	JUN 1-72	EMPIRIN #3	C	B	NO	8-211 SP	50	20
40	JUN 16-72	EMPIRIN #3	C	G	NO	9-482	24	6

6 months Rx = #40 Total Costs = $186.75 Average Rx Price = $4.67

PAID PRESCRIPTIONS
RUN DATE: APRIL 14, 1972

PATIENT PROFILE
TYPE:"INTERACTION"

PAGE NO.
9219

PATIENT NO. 00055 NAME: IRA A.

THERAPEUTIC CLASS	DATE OF SERVICE	DRUG & STRENGTH	PH'CY	M.D.	IN PATIENT	RX NO.	QUANTITY	DAYS' SUPPLY
77	DEC 23-70	COUMADIN 5 MG	A	A	NO	81-603	30	30
77	JAN 30-71	COUMADIN 2.5 MG	A	A	NO	82-080	50	50
77	FEB 18-71	COUMADIN 5 MG	A	A	NO	82-303	50	50
77	MAR 22-71	COUMADIN 2.5 MG	A	A	NO	11-099	50	50
77	MAY 14-71	COUMADIN 2.5 MG	A	A	NO	14-389	50	50
41	FEB 18-71	Na SALICYLATE 600 MG	A	A	NO	82-299	100	30
41	MAY 14-71	Na SALICYLATE 600 MG	A	A	NO	82-299	100	30
42	MAY 27-71	BUTAZOLIDIN 100MG	A	A	NO	83-427	60	27
47	MAY 27-71	NOCTEC CAP. 500 MG	A	A	NO	83-426	30	30
51	MAY 26-71	H.C. 0.25%	A	A	NO	74-318	15	30

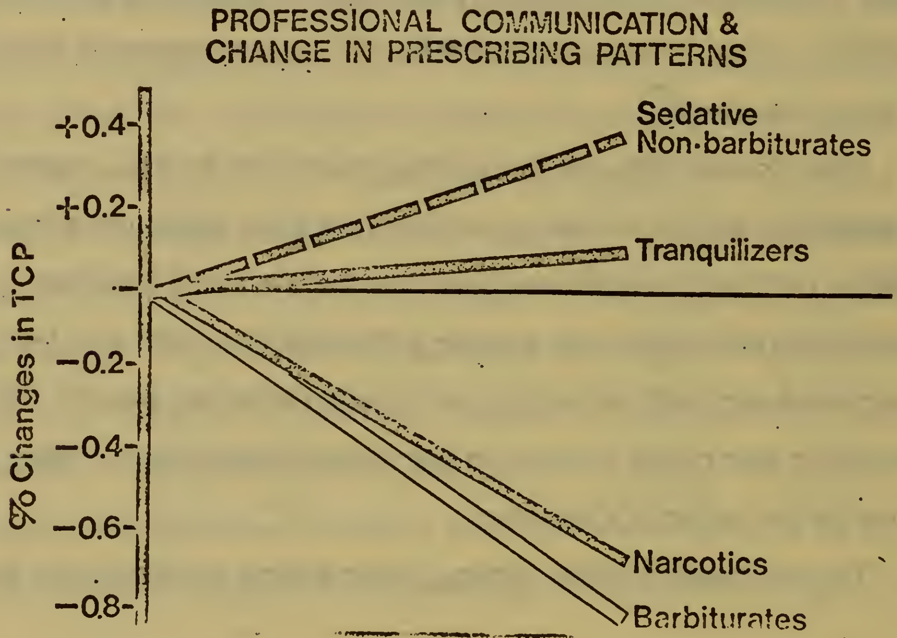
Communication of data is the most difficult task of drug review. The historical division of labor between the physician's prescribing and the pharmacist's dispensing made necessary the creation of a multidisciplinary drug utilization review committee. In San Joaquin this committee is composed of four pharmacists and one physician. The committee determines if there are cases of possible abuses which might be patient-, physician-, or pharmacist-oriented. Letters challenging unusual practices are sent to the physicians and pharmacists involved. These are always accompanied by a copy of the patient's six-month drug history and are addressed individually on committee letterhead stationery. Letters directed to the physicians are signed by the physician member of the committee, and letters directed to pharmacists are signed by the pharmacist secretary of the committee. If the outstanding success of our program is to be appreciated, it is due to this unique communication network which includes a feedback mechanism from all practitioners under review. An immediate result of these peer review activities is the 12.1% cost savings derived from the correction of wasteful practices which was experienced the first year.

The ultimate goal of a well-organized drug utilization review program is to change patterns of practice in a community of physicians and pharmacists by peer communication techniques in order to conserve resources without detriment to the patient or undue interference with the professional prerogatives of the practitioners. We can document that the cost savings due to this peer communication can be substantial. Out of a sample of 60 cases, 17 showed definite changes in prescribing and dispensing patterns resulting in yearly estimated savings of $1,111.20 or an average of $18.52 per patient per year.(3)

Since October 1970, two months after the start of our drug program, the utilization rate and cost per prescription in the San Joaquin area have remained continually considerably lower than the rest of the State even though many restrictions, such as prior authorization for more than two prescriptions per month per patient, were never needed nor enacted. We feel that our peer review process has been largely responsible for maintaining the good patterns of practice.

The San Joaquin Medical Society, having become concerned with the number of prescribed narcotics and barbiturates found in the possession of arrested juveniles, has utilized this drug monitoring program of patient profiles and therapeutic class profiles as part of a community drug abuse program. These patient profiles can demonstrate the patient who might be supplying part of the illicit market through receiving large quantities of addictive drugs. The area TCP profile can also monitor the effects of coordinated efforts to change the availability of harmful drugs.

In October 1971 the San Joaquin County Medical Society sent a letter to each physician of the medical community expressing the need that he re-evaluate his prescribing practices in regards to barbiturates, narcotics, and psychotropic drugs. No other attempt was made to alter or interfere



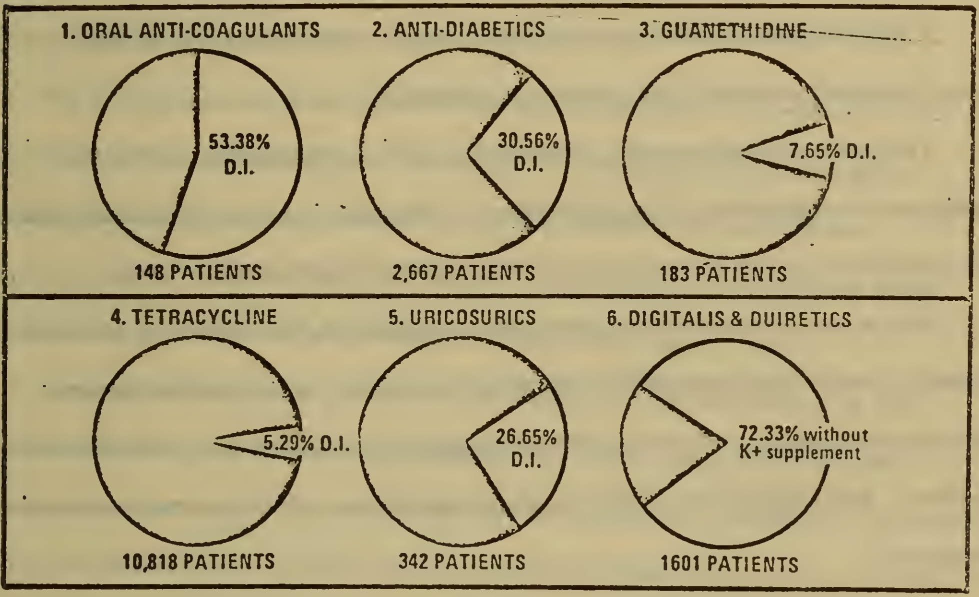
with the prescribing activity of the physicians. At the end of eight months, the community's therapeutic class profiles for these drugs were evaluated and compared to the profiles prior to the letter. In the mood-altering drug category, no appreciable effect was noted. However, there was a decrease of 0.7% in narcotic analgesics; in sedative barbiturates a decrease of 0.8% was noted, and non-barbiturate sedatives increased by 0.4%. This corresponds to a decrease of 2800 prescriptions for narcotics, 3200 prescriptions for barbiturates, and a subsequent increase of 1600 non-barbiturate sedative prescriptions. By using statistical T tests on the data, one calculates that the probability of this occurring by chance is less than 1/1000. It must be stressed that this involves only the Medi-Cal population and if the same prescription trend held true for the remainder of the community, a considerable decrease of physician-prescribed narcotics and barbiturates would result.

The use of the exceptional patient profile leads to the most significant improvement in the quality of medical care. It is with this profile that the patient receiving undue drug therapy is discovered. When such a patient profile is selected by the committee, the letters are sent to the physicians and pharmacists involved accompanied by a copy of the profile which is usually adequate to change the practice. However when we encounter a patient who is going from physician to physician and pharmacist to pharmacist, a "shopper," it is difficult to change his pattern of treatment. In the future, professional energies should be directed toward influencing the various public assistance programs to allow us to restrict such individuals to the services of a single physician and pharmacist.

The long-term effect of peer communication is an educational one and cannot be immediately measured. By on-going review and documentation of drug-dispensing activities and the utilization of the communication network, a dynamic process of continuous education occurs. The impact of the complete documentation of a patient profile on practicing professionals cannot be overemphasized. It is difficult for practitioners to ignore the persuasive prodding by their peers when problems are identified and displayed.

The educational aspect of our program can be directed to the prevention of adverse drug reactions (ADR's). One fourth of all ADR's result from drug-drug interactions. Because of our concern, and as an extension of, our original program, we are now expanding our peer review activities into the area of preventing known drug-drug interactions. In order to measure the size of the problem, we realized the need to quantify the magnitude of potential drug-drug interactions in our ambulatory patient population consisting of 41,996 Medi-Cal patients and involving 417,928 prescriptions for a one-year period.(4) The drug interaction rate per patient was calculated by dividing the number of patients receiving two or more interacting drugs by the number of patients receiving drugs subject to interaction. If two or more drug interactions were listed on a patient profile for a span of time which indicated that they were concurrently prescribed and dispensed, the computer selectively furnished a 12-month drug history for that specific patient.

The classes of drugs studied were anticoagulants, hypoglycemics, guanathidine, tetracycline, uricosurics, and digitalis in conjunction with diuretics. 7.57% of the patients were found to have been exposed to potential drug-drug interactions. In a population of out-patients receiving their medical care from the clinic at the University of Southern California - Los Angeles County Medical Center, Maronde using different criteria also demonstrated that the magnitude of potential drug-drug interactions in his universe was of the order of 7.5%. (5)



One of the more critical drug interactions involves oral anticoagulant drugs. Our computer data was checked for potential interactions between coumarins and hypnotics, salicylate analgesics, Atromid-S$^{(R)}$, quinine, and quinidine. 148 patients received prescriptions containing coumarins. 79 patients or 53.38% also received prescriptions for one or more of these potential interacting drugs.

The effect of oral hypoglycemic agents and insulin may be changed by a variety of medications, either by antagonism or enhancement of the antidiabetic activity. Of these drugs we have selected sulfonamides, salicylates, chloramphenicol, Inderal$^{(R)}$, and Butazolidin$^{(R)}$.

2,667 patients received antidiabetic drugs. 815 patients or 30.56% also received potentially interacting substances.

Tricyclic antidepressants, when taken with guanethidine, inhibit the antihypertensive effects of guanethidine. 183 patients received guanethidine. 14 patients or 7.65% received tricyclic antidepressants concurrently.

It is a well known fact that calcium, magnesium, or aluminum antacids greatly impair the absorption of tetracycline resulting in lowered serum tetracycline levels. 10,818 patients received prescriptions for oral tetracycline. 572 patients or 5.29% received cationic-containing antacids simultaneously.

Salicylates antagonize the uricosuric effect of the probenecid class of benefit of the Medi-Cal program (codeine and aspirin, Darvon$^{(R)}$ and aspirin, sodium salicylate, and Percodan$^{(R)}$). We are unable to measure the quantity of self-administered salicylates these same patients consumed.

The combination of potassium-wasting diuretics and digitalis glycosides predisposes to digitalis toxicity and multiple cardiac arrhythmias. This is a classic well known interaction. In these cases, digitalis toxicity may be prevented by the concurrent use of potassium supplementation. The patients receiving both potassium-depleting diuretics and digitalis were reviewed for the absence of prescribed potassium. 1,061 patients received digitalis and hypokalemic diuretics. 1,158 patients or 72.33% did not receive prescribed potassium supplementation.

An analysis of our data reveals that the incidence of drug-drug interactions was of such magnitude to warrant our concern. We are now programming the computer to develop on-going programs to reveal these interactions and to utilize our peer review techniques to communicate these data to the physicians and pharmacists involved with patient care.

Another drug-related problem which deserves more attention is the prevalence of common adverse drug reactions. If any prevention of these reactions is to occur, it will occur through an educational program. Adverse drug reactions are events which can be qualified as having unintended, unanticipated, and undesired effects on a patient. These effects are related to ordinary drug use both prescribed and self-administered but not involved with abuse due to alcohol or illicit drugs.

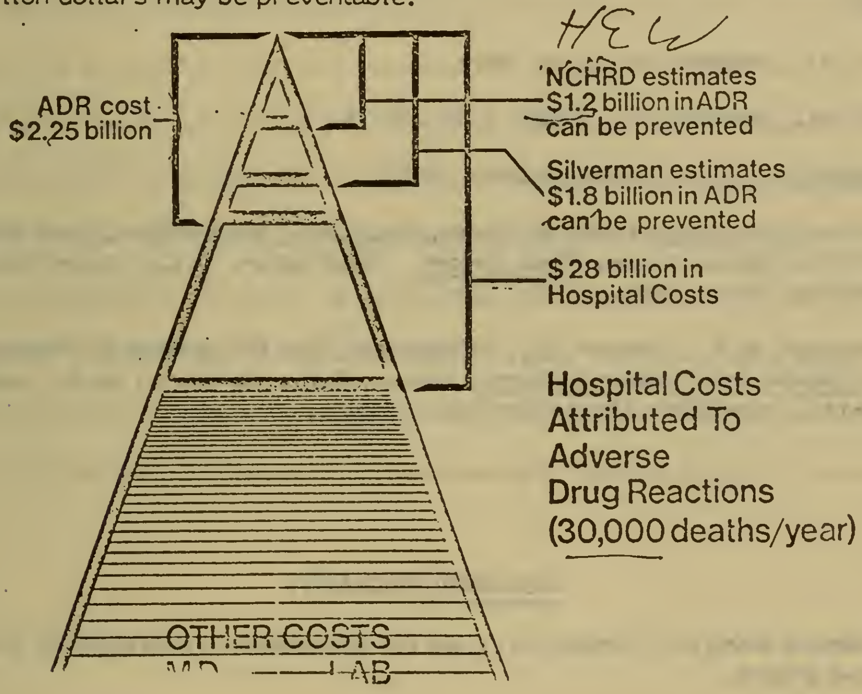
Silverman estimates that deaths from ADR's are in the range of 29,000 to 30,000 per year or approximately the same mortality rate as cancer of the breast. Melmon (6) calculates that 20%-30% of these ADR's cannot be prevented and these are mainly due to individual patient idiosyncrasies and allergies or unknown drug toxicities. He claims the remaining 70%-80% of these reactions are both predictable and preventable. Various investigators have attempted to identify and quantify the adverse drug reaction problem.(7)

Most of our ambulatory patients are usually exposed to less than six drugs at one time. During hospitalization the risk of being exposed to ADR's is increased dramatically since during a hospital stay the average number of drugs administered is ten but this number can often be as high as 35. With five or fewer drugs, chances are that 5% of the patients will be recognized as undergoing an adverse drug reaction serious enough to cause a change in therapy; if the patient is exposed to 20 drugs, the possibility of an adverse drug reaction increases exponentially to 45%. (8)

We can estimate that adverse drug reactions:

1. account for 4% to 7% of all hospital admissions
2. occur in 10% to 18% of all patients in a medical service
3. require prolonged hospitalization (approximately twice as long)(9)

The National Center for Health Research and Development of HEW estimates that there are approximately 1.5 million hospital admissions due to ADR's annually. In 1970 the average length of stay in a community hospital was 8.2 days; (10) thus 12.3 million patient days are directly attributable to ADR's. If we calculate just the costs of hospitalizations at $90.00 per day, we arrive at a figure of $ 1.107 billion dollars of which 80% or 886 million dollars may be preventable by proper drug usage. Many other investigators believe that these estimates are too low. They calculate that one-seventh of all hospital days are attributable to adverse drug reactions. (11) Silverman and Lee, in a book soon to be published, have established the national hospital bill due to ADR's at 2.25 billion dollars of which 80% or 1.8 billion dollars may be preventable.



Hospital Costs Attributed To Adverse Drug Reactions (30,000 deaths/year)

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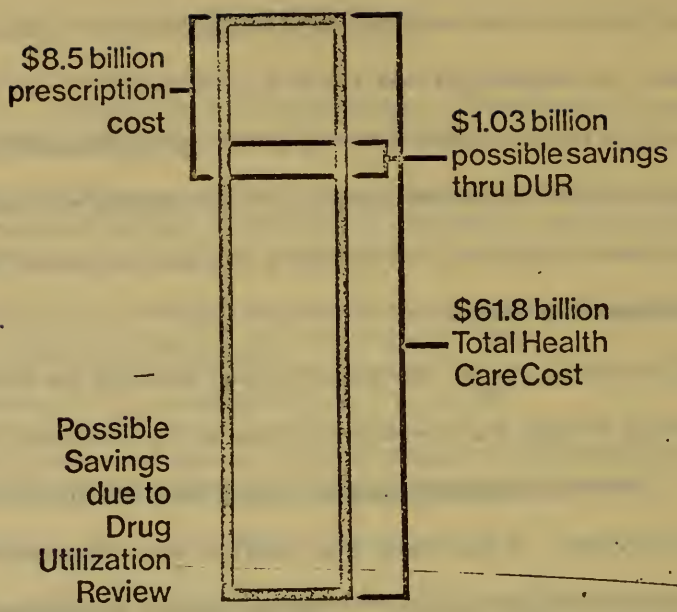
ACKNOWLEDGMENT

The authors thank Dr. Kenneth W. Lem for assistance in coordinating the data and graphs.

If we add the prolonged hospital stays which have been documented as being doubled, our estimate is that 1.2 to 1.8 billion dollars can conservatively be saved in hospital costs alone by proper drug utilization and control. This is just the visible tip of the iceberg, and no reliable estimates are available for other costs such as laboratory charges, physician fees, and the patients' economic losses.

For the last three years, Maronde has been studying the patterns of drugs dispensed through the out-patient clinics at the University of Southern California - Los Angeles County Medical Center with the aid of a computer surveillance program. It was found that 12.4% of the prescriptions represented orders for excessive quantities. (12) By controlling these excessive quantities, 10% of the drug expenditures can be saved without compromising the quality of the drug care and in fact improving it. It is remarkable that our experience in the San Joaquin area reflects savings in the drug premium in the same range. By submitting prescriptions to Committee review, we have been able to save 12% of the premium. If we project this possible 12% savings to the national drug bill for prescribed and dispensed drugs estimated by Silverman and Lee at 8.5 billion dollars per year, we arrive at a total of $1.03 billion of unnecessary expenditures in the costs of medication alone which can be saved by effective drug surveillance programs and peer review.


$8.5 billion prescription cost
$1.03 billion possible savings thru DUR
$61.8 billion Total Health Care Cost
Possible Savings due to Drug Utilization Review

It is possible to achieve these savings without disruption of the present health system if we realize that during the last forty years we have witnessed a "knowledge and technical explosion" and that it is no longer possible for any single individual to become truly expert or to remain current within the mass of information originating from various scientific specialty fields but that computer technology can be utilized to record and document current patterns of treatment within a community and communication techniques can be utilized to maintain the information base of clinicians wherever they practice.

We have described the San Joaquin experience with our multidisciplinary drug review program. We have projected the potential savings which can accrue nationally through better utilization of available resources. It is our firm belief that by using these same techniques you can change the present national drug delivery system from one of benevolent neglect to one of active professional concern for the benefit of our patients.

Dr. TALLEY. If we know that the national prescribing—I have to look at my figures to get them fresh.

Senator KENNEDY. I think they are at page 28.

Dr. TALLEY. Thank you. $8.5 million per year is the figure. With our program with over 12.1 percent savings which we will get to later in my testimony, we would come out with $1.03 billion possible savings in drug utilization.

The other two things have to do with this type of economics.

Senator KENNEDY. It seems to me that there is such a spirit of economy in the country, looking for ways of cutting back on programs, it seems to me that that is a pretty impressive way to save a billion dollars.

Dr. HARRINGTON. I would like to make sure that you are aware that this section of this report has to do with just dollar savings. It has nothing to do with drug quality control. This is step one of what he is going to talk about, and it is not the quality problem.

Senator KENNEDY. Yes.

Dr. TALLEY. The refill control report is designed to check the elapsed time between refills according to the days' supply of medication. It also differentiates between in-latients and ambulatory patients as there are some quantity formulary restrictions imposed on patients in nursing homes. The reviewer challenges any prescription which in his judgment is refilled too soon, according to the physician's directions. If the pharmacist can document an authorized dosage change or other valid reason, the claim is passed for payment, otherwise payment is automatically denied.

The inappropriate quantity report lists various drugs which fall outside certain criteria which were set as being either too large or too small quantities based on current pharmacological knowledge. This report is a valuable tool to reveal instances of prescription splitting, too frequent renewal of chronic medication, short counts, billings for prescriptions not dispensed, and "loading" patients prior to program changes.

The therapeutic class profile is one of the most useful monitors of current drug use. All drugs dispensed in the San Joaquin program are recorded on a bi-monthly basis according to 99 therapeutic categories and by individual drugs for each pharmacy, physician, and patient. These profiles on drug utilization for each therapeutic class are a valuable measure of drug use and an indicator of possible inappropriate prescribing, dispensing, and drug-taking.

Given a long enough period of time and enough accumulated data, it has been found that most pharmacies have a similar percentage activity in each therapeutic class of drug, since patients are all subject to similar diseases, and are treated by similar therapeutic procedures within a given community. We monitor the Therapeutic Class Profile (TCP) for each physician and pharmacy compared to the area TCP.

Senator KENNEDY. You are doing each physician, each pharmacy, each patient, as I understand.

Dr. TALLEY. Not on TCP, but for each pharmacy and each physician, yes.

It is very simple, if you write 100 prescriptions and seven are for narcotics, you have a therapeutic class profile of narcotics of 7 percent. For our program I think about 7 percent is correct for the community for narcotics.

If you find there is a profile of 17 percent, this looks suspicious, the computer will pick this up. I do not have to look at each one of these.

Senator KENNEDY. That principle seems to be adaptable to national use.

Dr. TALLEY. It depends upon whether there is a way to accumulate the data. If it is on a prepaid program, yes, then you have a handle to gather this type of data.

Senator KENNEDY. So in this instance then, the prepaid system is better for quality?

Dr. TALLEY. For drugs under this program, yes.

Dr. HARRINGTON. Senator, in our summation I am going to get into what we call "model treatment" which gets into the use of the computer in much more sophisticated form than we do now, which is applicable nationally.

Senator KENNEDY. All right. Let me just follow up.

Are the doctors satisfied? I know both of you are practicing physicians.

Dr. TALLEY. I think for the most part, yes. I think that we help; we do not hinder. I will get into this also as we go along.

Senator KENNEDY. All right.

Dr. TALLEY. The exceptional patient report is an automatic claim review mechanism which furnishes examples of possible abuses which might be patient-, pharmacy-, drug-, or physician-oriented. An individual patient profile is furnished automatically if the drug utilization falls within certain parameters.

Any patient who receives the same drug from two pharmacists on the same date, any patient who receives services from our or more pharmacists in a 32-day period, and any patient who receives more than four prescriptions in one therapeutic category will appear on this exceptional patient profile.

The exceptional patient profiles are furnished to the Drug Utilization Review Committee members for review, and it decides if these are profiles of patients legitimately requiring much pharmaceutical support, or if they are indicative of patient-oriented abuses of recipients shopping for physician and pharmacist services to procure unwarranted quantities of drugs. The committee also checks for physician-oriented abuses which usually involve poor control of therapy through the prescribing of too many drugs in the same therapeutic category, or drugs which interact undesirably when taken together.

Communication of data is the most difficult task of drug review. The historical division of labor between the physician's prescribing and the pharmacist's dispensing made necessary the creation of a multidisciplinary Drug Utilization Review committee. In San Joaquin, this committee is composed of four pharmacists and one physician. I am not the physician.

The committee determines whether there are cases of possible abuses which might be patient-, physician-, or pharmacist-based. Letters challenging unusual practices are sent to the physicians and pharmacists involved. These are always accompanied by a copy of the patient's six-month drug history, are addressed individually on committee letterhead stationery and are signed by a professional peer.

If the success of our program is due to any major factor, it is this unique communication network which includes a feedback mechanism from all practitioners under review. An immediate result of these peer review activities has been the 12.1 per cent cost savings derived from the correction of wasteful practices which was experienced in the first year.

Since October 1970, two months after the start of our drug program, the utilization rate and cost per prescription in the San Joaquim area have remained consistently and substantially lower than the rest of the state, even though many restrictions, such as prior authorization for more than two prescriptions per month per patient, were never needed or enacted.

Senator KENNEDY. What you are saying is that good practice is economical.

Dr. TALLEY. That is correct.

We feel that our peer review activity and physician-pharmacist involvement have been largely responsible for maintaining good patterns of practice.

The use of the exceptional patient profile leads to the most significant improvement in the quality of medical care. It is with this profile that the patient receiving undue drug therapy is discovered. When such a patient profile is selected by the committee, the letters are sent to the physicians and pharmacists involved, accompanied by a copy of the profile. This process is usually adequate to change the practice. However, when we encounter a patient who is going from physician to physician and from pharmacist to pharmacist, a "shopper", it is difficult to change his pattern of behavior.

At this stage of the development of our program, we are directing the educational aspect toward the problem of drug-drug interactions, wherein the patient may simultaneously be taking two or more incompatible drugs. We studied our data and determined that 7.57 per cent of the 41,996 patients receiving 417,928 prescriptions in a one year period were involved with potential drug-drug interactions. No clinical evaluation of these data has been undertaken, however, and we are not at this point able to document any deleterious effects. These data are consistent with a University of Southern California study of ambulatory patients.

We are now communicating these data to the physicians and pharmacists involved in the patient's care. In the future, we will report the impact of our communications system upon this problem.

Senator KENNEDY. May I ask you in this review do you find out if your doctors are using experimental drugs?

Dr. TALLEY. We could. I know of no example of it, but we could query the computer on any drug. I do not have the data. I really do not know.

Senator KENNEDY. But at least that information could be developed through your computerization.

Dr. HARRINGTON. Unfortunately we do not know what are experimental drugs. This is not publicized to the general public as a rule. In other words, we do not use DES—I am a gynecologist in charge of the operation of the program at San Joaquin General Hospital. We have not used DES, but I was not until today aware that it was experimental. So there is a great lack of communication between here and us.

Senator KENNEDY. Is this because the FDA says it is not responsible for it, and this is part of the problem? Here you are, a distinguished practicing physician, who is enormously aware of the problem, but you are unaware DES is considered experimental.

Dr. TALLEY. The long term effect of peer communication is an educational one and cannot be immediately measured. By on-going review and documentation of drug-dispensing activities and the utilization of the communication network, a dynamic process of continuous education occurs. The impact of the complete documentation of a patient profile on practicing professionals cannot be over-emphasized. It is difficult for practitioners to ignore the persuasive prodding by their peers when problems are identified and displayed.

In summary, the ultimate goal of a well-organized drug utilization review program is to change patterns of practice in a community of physicians and pharmacists by peer communication technics in order to assure quality of care and cost optimization.

The San Joaquin experience suggests that a program of systematically gathered drug data, subjected to peer review, can have a significant effect on the quality and cost of drug therapy. It is our belief that the essential ingredient of such a program is the review of the practitioners by their peers.

Dr. HARRINGTON. I would like now to summarize and go a little bit into our model treatment.

I am sure that you can see by Dr. Talley's presentation that considerable progress can be made in peer drug review by even a rather primitive computer system. Dr. Talley gets upset when I call it primitive computer system, but it really is based mostly on simple components for on-going review and more detailed system of retrospective exceptional reporting.

It is obvious that additional benefits will accrue particularly in large communities by more detailed methods of on-going review. Such a system is under development and should be available in about 6 months.

Now I will speak of model treatment. Because of the attorney general in California, the welfare department, and the department of health care services, some years ago set up a feasibility study with Lockheed. They spent a million and a half dollars to determine whether the computer could be programed for peer review. Lockheed studied our program in San Joaquin and some other foundations in detail and said, yes.

California then set up a study which has been completed now for the actual programing of peer review, and two communities are at the present time in a prototype study: San Diego and Santa Clara.

The Western Conference of Foundations have had a subcontract to do the professional input in the professional components of this peer review system, and we are watching this rather carefully.

Secondarily HEW funded a further computer development, and we are at the present time testing this system.

The parameters of care in California need national surveillance. We have met already with the American College of Physicians, having some nine meetings with the American College of Physicians people from all over the country, to obtain information as to necessary visits, laboratory work, X-ray, drugs, injectibles that are necessary for all of the various diseases under their peer review.

We have also met seven times with the American College of Surgeons with their committees, going over the information as to what surgical procedures are necessary. We have met during a two-day meeting with the American College of Obstetrics and Gynecology, and with the American Society of Internal Medicine.

We have now finished all of these meetings and have subjected the parameters of care that were developed in California to a very comprehensive scrutiny by these rather prestigious organizations, as to what should be in the computer for study.

We are now trying to develop a meeting with the American Academy of General Practice to get input from them, and then our programs will be complete. This obviously will be a forever program. It will have to be modified constantly, the parameters changed, added, and so forth.

Under this program a claim would come in, or a statement of service would come in, to the computer center, and it would go directly through the programing unit.

If it were rejected, it would come out at the end with a patient profile which Dr. Talley has just stated we use, and it would say this claim has been rejected because there are too many office visits, too many injections or laboratory work is not necessary.

This then would be sent to the peer review center—or if there were drugs ordered that do not relate to the diagnosis involved.

These would be sent to the center for study by their peers, and then corrected information would be sent back, and the provider would be paid on that basis. Then the necessary education would be given to the individual who was at fault in this particular area.

Dr. Talley sometime back came up with the problem on underutilization. We are now programing the computer for such things. If a person calls him because he has diarrhea, indigestion, and receives over the phone from many different doctors—perhaps because he calls a different one at a different time—Pepto Bismal or whatever, if this continues over a 3-month period of time, the computer will reject this, remand this for review, and it will ask what is really wrong with this patient? Has he seen a doctor? If so, what has the doctor done to come up with a diagnosis?

Senator KENNEDY. Do the doctors really not resent this? Is this not a computer telling them how to practice medicine?

Dr. HARRINGTON. No, sir. You notice I changed the word from reject to remand. This was suggested by Dr. Hanlon of the American College of Surgeons.

The reason is that the computer only takes medical information, remands that claim for further study by the professional or by the peer involved, and the doctors do not resent this.

As a matter of fact, all the medical organizations involved are anxious to see the computer runouts so they can learn how various diseases are treated in various parts of the country, and see what kind of treatment is done.

But getting to the drug program, we are at the present time having conversations with two computer companies trying to develop a CRT for use in the pharmacy whereby the computer could be queried and make sure that the actions would not occur, make sure that drug reactions which Dr. Talley has been working so hard on, make sure that overutilization of drugs is not carried out.

If the CRT is not available at least the computer could reject it or remand it immediately on the second prescription, or if the problem occurred in the matter of a week or ten days would pass out this kind of thing.

So what we are doing at the present time then is putting all of our peer review knowledge into the computer so that the computer can then do the work on massive scale.

What we have done in San Joaquin could not be done in Baltimore or New York.

That is the end of our testimony.

Senator KENNEDY. Why could it not be?

Dr. HARRINGTON. The on-going part would be impossible. Take, for instance, we see 45,000 prescriptions per month. It is impossible to do a manual review in a community as large as Baltimore on prescriptions.

The hospital review is simple, but without a computer you cannot do these things. This is why this model program is so important.

Senator KENNEDY. How many are taking advantage of it?

Dr. HARRINGTON. It is not ready yet. There are a lot of computer companies anxious to give this a try.

Senator KENNEDY. As far as Baltimore and New York, if they were able to get it on computers——

Dr. HARRINGTON. If they were, for instance, we could at the present time in our computer put in a stop so that any prescription for DES that would come through would be rejected for study as to why it was given. The person would have taken it once, but only once, so I mean the computerization in the drug program I think is extremely important.

Senator KENNEDY. Why cannot the government do this? We just heard the head of the Food and Drug Administration talk about widespread use of DES; he was enormously alarmed. We hear testimony about the use of DES in these medical centers. We hear from a researcher about its status as a cancer-causing agent, and then we hear you say it would be a cinch to identify this kind of problem.

What are we missing here?

Dr. HARRINGTON. It depends upon let us say, how the drug is prescribed. In other words, in our area of approximately two-thirds of all the people in our area we receive their drug claims. Now, take for instance, the University of Michigan. If they are prescribing it through their own area, there would be nobody who would be able to check on them on this.

It depends on who is handling the payment and the fiscal problems of payment for the services.

Senator KENNEDY. But if you know how to do it, why doesn't the Food and Drug Administration?

Dr. HARRINGTON. You know the wheel is just being built and we are adding spokes to it. We have been fooling around with this thing for about 14 years. We have quite a bit of background information that we are now capable of putting into the computer.

We have talked to some of the other people that are not only in the computer area, and some of our fiscal intermediaries who do not at the present time have a separate coding. They use one number that includes all shots.

We have broken down our shots so we can tell you how many shots of penicillin a doctor is using.

So it depends upon the statute of this information, and then the desire for them to do it.

Senator KENNEDY. You are the best example that all knowledge is not in Washington.

Dr. HARRINGTON. This DES thing reminds me of what Dr. Osler said: "Be not the first to take on a new product, and be not the last to discard the old."

On the other hand I would like to point out that the abortion rate is climbing and going up and up, and without DES perhaps you are going to have a continued increase in the abortion rate. I think you all have to think about whether it is better to abort the six who became pregnant under DES or to abort the 114 who would have been pregnant otherwise.

Senator KENNEDY. I agree with you.

Let me ask, Doctor, why you have not heard about DES?

Dr. HARRINGTON. Yes, I know all about it, but I did not realize that the Food and Drug was studying it. It has been available to us for years for different purposes.

Senator KENNEDY. For other purposes, but you did not know——

Dr. HARRINGTON. But knowing what I know about DES, we have never used it.

Senator KENNEDY. What does the AMA think of your system? Have they been out to study it?

Dr. HARRINGTON. Yes. As a matter of fact, they have referred certain counties that have had problems to us for consultation, and I am sure that the AMA, being the parent organization for the people who have been thrown out of the John Birch Society for being too far to the right, as well as people like myself who they consider too far to the left—and the AMA has to be home for both people—it makes it a difficult posture for them to walk, so we try to help them out in as progressive a way as we can.

Senator KENNEDY. I do not know whether you want me to condemn you or applaud you today. [Laughter.]

Dr. HARRINGTON. We have three of their board of trustees on our American Association of Foundations, and I think they are now a little more aware of what we are doing, and I think the attitude is a little more cooperative.

Senator KENNEDY. What you have found here, Dr. Harrington and Dr. Talley, seems to have more applicability. Do you think the situation that exists in San Joaquin exists in other communities, maybe in California, and across the country?

Dr. TALLEY. If you are referring to drug prescription habits, yes, I think it is very typical. I think San Joaquin is a typical community. I think there are many patients who create the problems, and doctors and pharmacists create the problems. I think all these problems need to be looked at, and I think the computer is the way to look at them, and the way to give the information back to the physicians so maybe there will be a change.

Senator KENNEDY. You talk a little about the adverse drug reaction. I think in that statement that you made in Georgia you mentioned a figure of some 30,000 deaths a year, I understand.

Dr. TALLEY. This is a quotation of adverse drug reactions from the public health department. Approximately 30,000 deaths a year are created by adverse drug reactions.

Senator KENNEDY. Those are HEW figures?

Dr. TALLEY. Right.

Senator KENNEDY. We have been through your computer review. Do you think that would cut that in half? Do you think through a computerization program that would be a realistic goal?

Dr. TALLEY. I cannot really answer that question. I would feel there would be some death certainly.

Certain of the drug interactions that we have pointed out—we had one which was very serious and that was a combination of prescriptions that may be coming from two or three different physicians, not just one physician in prescribing.

Sometimes when you ask a patient, Are you taking any medicine, they say, no, and when you find they are taking a sleeping pill, you get the answer, A sleeping pill, that is not a medicine.

It is a communications problem from patient to physician which sometimes will block this information so they are not cognizant of drug interactions. If there are two physicians prescribing, you have some potential danger.

I believe with this type of information and feedback, when the pharmacy can query the computer to ask if there is a potential drug interaction or reason for not giving it, and the answer will come back instantaneously, the communication between the physician and pharmacist will then take place. That may be in the dream world, but it is in the future and something to think about.

Senator KENNEDY. You saved $1.2 billion in double billing.

Dr. TALLEY. And drug review in general.

Senator KENNEDY. Can you save us a little bit on the adverse drug reaction?

Dr. TALLEY. This was in Dr. Mellman's article in the New England Journal of Medicine. Just taking hospital days which were felt due to adverse drug reactions, there is probably another $2 billion total saving, not talking about all the other potential savings within this area. So there is a tremendous possibility of saving more dollars in the health care dollar created by adverse drug reaction.

Senator KENNEDY. You could build a lot of health centers with that.

Dr. HARRINGTON. Senator Kennedy, I think it would only be fair to say when the fiscal intermediaries first got into this they were overwhelmed; they did not get into duplicate billing, and it took some years to do this.

I think that probably all of the good fiscal intermediaries now do have duplicate controls in their systems, so that in a system I was talking about the medical savings that could be done, that could be obtained by insisting that these have duplicate controls in their system, if they do not already have them.

Senator KENNEDY. Is it your feeling it is important that we develop more effective systems of monitoring the use of drugs in this country on the national level?

Dr. Talley. I would think that would be advantageous, yes.

Dr. Harrington. I think this is one of the good reasons for putting drugs into Medicare, because it does allow the monitoring of the drugs in the program, to make sure what the oldsters are getting. If they find them on the free market, there is no way of monitoring, so I think drug programs are something that should be considered with favor.

Senator Kennedy. Of course in Medicare they would be included in the Health Security Act as well. We are not here to talk about that particular program.

Dr. Harrington. We are sorry you cannot be with us in Tahoe to talk to you about it, but maybe we can catch you at a later date.

Senator Kennedy. I want to thank you very much. You are enormously imaginative and the programs you have developed are a great credit to the people of the medical profession who have supported it and carried it through, and I think we can profit enormously across the country from what you have done.

I want to thank you very much for your appearance here. I am sure we will be drawing on your experience in the future in trying to work with you so that we can make sure the savings and the benefits that you have been so effective in achieving for the people in California may be realized nationwide.

Our fourth witness this morning is James F. Goddard, former Commissioner of the Food and Drug Administration and currently a consultant to the Ormont Drug Company. It is a pleasure to see you again, Dr. Goddard. We appreciate your understanding the necessary change in the program.

STATEMENT OF JAMES L. GODDARD, M.D., CHAIRMAN OF THE BOARD, ORMONT DRUG & CHEMICAL CO., ENGLEWOOD, N.J.

Dr. Goddard. Mr. Chairman, it is good to see you again.

I am James L. Goddard, M.D., Chairman of the Board of Ormont Drug and Chemical Company, Englewood, New Jersey. In recent years the attention of those interested in the field of pharmaceuticals has been directed on several occasions to the issues surrounding the "unapproved" use of marketed drugs or chemicals. On several occasions congressional committees have raised the issue during hearings on related matters but this is, to my knowledge, the first hearing devoted solely to the subject.

The issue is a complex one—with ramifications relating to the quality of patient care, the role of a federal agency vis-a-vis the medical profession, the responsibilities of the pharmaceutical firms involved, and the legal liabilities of physicians who use marketed drugs for unlabeled uses. In the short time available to me I cannot cover all aspects of this important subject and I will therefore limit my remarks to the issues of effect on patient care and what steps can be taken which may improve the situation.

With respect to patient care, my concerns are related to the potential dangers that may rise as a result of using marketed drugs for unlabeled uses. There is the danger that incomplete information will denigrate the quality of care. Ordinarily the physician has rather comprehensive information available to him from a variety of sources.

The major ones are:

(a) The professional literature

(b) The package circular

(c) Physicians desk reference

(d) AMA Handbook of Drugs

(e) Promotional material from manufacturers

When marketed drugs are used for unlabeled uses it is apparent that existing information will not be directly applicable, and that the professional literature becomes the sole source of printed information. This could be sufficient were it not for the fact that much of the "unapproved" use is based on word of mouth "testimonials" rather than careful study of material presented in a journal. An equally significant drawback is that usage is often based on a single uncorroborated study rather than a number of well controlled studies.

This means that the physician really is unable to judge comparative efficacy; have any significant knowledge as to side effects which might be unique in relation to the "unlabeled" indication; that drug interactions could occur and as a result the patient care would suffer.

I concede all of these may not occur and the patient may indeed benefit—as I also concede the attending physician must be the one to make the ultimate judgment as to which medication for which condition.

What then can be or should be done? I would suggest the following:

1. By FDA. (a) Under existing authority very little could be done. FDA should not get involved in supervising medical practice. The problem would be lessened if FDA were more responsive to well documented studies demonstrating effectiveness for new uses.

Senator KENNEDY. Why is that? Why are they not responsive?

Dr. GODDARD. There are many reasons. As you well know, Senator, the problem of getting well controlled studies carried out is mainly that the FDA does not have funds for research on its own initiative.

When I was Commissioner I suggested to the Congress we have funds made available to establish clinical pharmacology centers in major universities, so that when problems of significance arose which were not of economic substance sufficient to attract investment capital from the pharmaceutical industry, the consumer could be protected by having the problems studied in one of these centers.

I still believe that to be a valid approach to a small part of the problem. But the problem is basically, because the unlabeled use is often of very little economic value, and the firm holding the NDA, does not choose to invest in carrying out the necessary studies.

Senator KENNEDY. What was the response of Congress?

Dr. GODDARD. We did not get the money, Senator.

(b) Under new authority FDA could formally provide the manufacturer with the opportunity to assume the burden of proof and if declined by the manufacturer holding the NDA then any other manufacturer will do so, with proviso that a license must be issued by the first company and that royalties be paid. I am simply saying enforced licensing could be used as one approach; or another alternative would be the establishment of special clinical pharmacology centers underwritten by FDA grants could; after review by NAS–NRC be asked to undertake study of efficacy. Following this the drug would be available for manufacture by any company willing to pay royalties to the originating firm.

A second area is what could be done by the medical profession.

In the hospital I believe drug utilization committees should be formed to evaluate drug usage by physicians practicing within the hospital.

I was encouraged to hear the remarks in the statement of Dr. Harrington and Dr. Talley, because I believe they have indeed made a significant contribution for both in-hospital patients and ambulatory patients.

In the community, drug utilization review by Medicare-Medicaid organizations or by new mechanisms, e.g., one new mechanism would be available at such time that time sharing computers are widely utilized by M.D.'s in their office practice. Such a system is feasible today, and at a realistic cost but has not been implemented in any community. Many other benefits would become readily available which would be potentially of greater significance than monitoring drug usage.

I do think that such a system as an aside, Senator, would have substantial impact on the question of unlabeled usages of marketed drugs. It could also enhance the dissemination of information on marketing drugs, something I think that we could go a long way toward solving in some of these problems.

Thirdly, by state agencies. It would not be practical under existing or new authorities for state agencies to be involved directly related to this issue.

Overriding all that I have said is the urgent need for a significant change in the FDA New Drug Approval process. This is in no way criticism of the efforts of the FDA personnel who must operate under existing legislative mandates but rather a plea for substantial change in the law.

Specifically I would propose that the Congress direct the agency to establish in each recognized specialty, a scientific council comprised of non-governmental experts who would: (a) At the receipt of an IND review the application to determine worthwhileness of the proposed studies and the competence of the proposed investigators.

(b) Maintain surveillance over the IND throughout each phase periodically evaluating progress.

Senator KENNEDY. Can you really maintain surveillance?

Dr. GODDARD. I think you can more effectively than today's process. Keep in mind the three phases of the IND investigation: Phase 1, by one or two investigators who examine the use of the drug in subjects who do not have the disease the drug is intended for; Phase 2, by a handful of investigators who are highly skilled, who examine the use of drugs in patients using the drug on which you want to keep close surveillance; and Phase 3, when the drug is then used under the conditions of expected market uses. Here there may be several hundred investigators.

But it is my feeling that panels of experts of this type would know most of the competent investigators. They would have the opportunity to receive the reports that FDA now receives, and assess how the project is going, and how are the patients' interests being protected—are the subjects being properly informed? How well is the drug working?

I believe, therefore, it would be easy to recommend to the commissioner approval or disapproval at completion of Phase 3 and recommend amendments to original NDA's when new indications for use have been developed.

Such councils would have permanent secretariat assigned by FDA and would be of sufficient size that the process would not be unduly burdensome to any individual member. Further, there should be provided a special mechanism for appeal from an adverse action on the part of the commissioner. I would suggest that a select group from the NAS–NRC be available for such appeals and that this step be required prior to institution any adversary procedure through our federal courts.

I am well aware, Senator, of the fears such a proposal could arouse in the various interested parties. The manufacturers might well express concern with regard to "trade secrets". I would suggest that manufacturing processes which are the only trade secrets of significance that are involved, be separated and provided to FDA as they now are.

Consumers groups might express concern that undue pressure would be brought to bear on the scientific councils by drug manufacturers. I would suggest that the broad scale participation by scientists of high repute would along with periodic change of membership provide a large measure of protection.

Parenthetically I would add that it would bring out into the open much of which is now held secret in the files of the FDA, and I think insure a higher quality of scientific effort in the new drug process.

Congress might fear this would be an unwise delegation of responsibility. I would maintain it to be a highly necessary one, for government service can no longer attract and maintain an adequate body of scientific manpower. Such an approach would help assure critical evaluation of our nation's drugs by those most competent to make such judgments: practitioners and scientists involved in the care of patients and the study of drugs who are deemed by their peers to be the leading experts in their chosen fields.

There are many subtleties of such a proposal which are not suitable for presentation at this time. I do feel, however, that the "problems" of "unlabeled use" of a marketed drug could be more readily solved by this approach and at the same time we could enjoy the benefits of earlier approval of NDA's without any sacrifice of public safety.

Mr. Chairman, I would be happy to respond to your questions at this point.

Senator KENNEDY. Thank you very much, Dr. Goddard. Your statement has been most helpful.

We heard yesterday, as you may be aware, and again in an indirect way today, how things stand in the country—a physician being able to prescribe a drug for reasons other than the FDA has approved.

We have seen this in the use of Depo-Provera in the State of Tennessee. We heard of patients who had not given their informed consent, who had not been made aware of any of the risks involved, and in effect the department of health in Tennessee, or individual doctors, were able to set themselves above the Food and Drug Administration in deciding what is safe and could be used.

What is your reaction to this situation? What do you think can be realistically done to improve it?

Dr. GODDARD. Senator, realistically we are not going to get the kind of improvement that I sense you are seeking until we have a national health service, and a good data base, and a record that tracks the patient throughout his life.

If you have to ask me for one substantial step I could have my choice, I would choose the record that tracks the patient through life, and thus having the good data base available to the physician.

The San Joaquin report was a very interesting one because it confirms what I have maintained for the past several years, that you can bring to hear peer review; that the medical profession can do the job if it is properly organized.

The lack of organizational structure I think is the major barrier not our technology. If airlines can handle reservations—which is a very complicated technical problem for computers—we can handle hospital bed reservations, review drug interactions, and adverse reactions. We can predict these. We can answer the kinds of questions that were asked by the physician from New York today. We can quickly ascertain risks. We can do many things that are not possible today.

The data exists, Senator, but they are not readily available for analysis, and so I would say that what you are seeking would only be answered at that point in time.

Senator KENNEDY. Where is the responsibility of the drug companies? How does that fit in?

Dr. GODDARD. I feel of course that the drug companies have a responsibility to conduct good research to provide the physician with good information on their products to take every step that they reasonably can to assure that he is knowledgeable and informed.

A well developed system would permit the providing of information directly to the physician in his office, and do so in a way that I think it would be utilized and would materially affect the quality of medical care.

Physicians are human beings, just as all of us, and we know there are substantial problems in every field of endeavor today. But I would say that the one factor that changes performance of any professional group is the knowledge that others in that same profession are evaluating their performance.

To do so on a day by day basis, using the computer system, providing a peer review group with the facts, then giving the physician the information, making him aware that somebody is looking over his shoulder, I believe would do the job.

Also I believe the drug companies would welcome such a system because the good use of drugs, the proper use of drugs, it is in their interest too.

Senator KENNEDY. What can we do outside of enacting national health insurance?

Dr. GODDARD. I have suggested in my testimony that the Food and Drug Act be changed substantially. Philosophically it is a major change. I think it is an appropriate time to consider it.

We are between commissioners, and may I say I have watched Commissioner Edwards from a distance. I think he has done an excellent job in a difficult position. But I do think the time has come to make substantial change in the enabling legislation.

Senator **Kennedy**. Thank you very much, Dr. Goddard, for your very splendid testimony which will be enormously helpful. We want to thank you very much.

Our final witness this morning is Dr. Robert Veatch, Associate for Medical Ethics of the Hastings Center of the Institute of Society, Ethics and the Life Sciences.

Dr. Veatch, we are appreciative of the help you have given us in preparing these hearings, and are delighted to receive your testimony.

STATEMENT OF ROBERT VEATCH, PH. D., HASTINGS INSTITUTE, HASTINGS-ON-HUDSON, N.Y.

Dr. **Veatch**. Thank you, Senator. I will offer orally a shortened version of my prepared remarks.

Senator **Kennedy**. We will include your entire statement.

Dr. **Veatch**. Thank you.

Today's citizen can thank modern biomedical research for conquering a good deal of human suffering. Unfortunately, many of these victories have required risk and personal suffering on the part of both courageous volunteers and unwitting victims who were the first of our species to receive a new drug or undergo a new surgical procedure. The specialized knowledge and technological skill behind these victories have also created a new category of experts—experts who because they possess this particular knowledge and skill, have the authority to decide whether an experiment is to be made on a fellow human.

In 1966 a Harvard anesthesiologist shocked the biomedical research community by publishing in the *New England Journal of Medicine* the methods used in 22 experiments on human subjects involving unethical or questionably ethical procedures such as the withholding of chloramphenicol from 157 typhoid patients in order to study the relapse rate, X-ray studies of bladder function of normal babies less than 48 hours old, or the insertions of tubes and needles into the hearts of normal and ill patients in order to increase scientific knowledge.

The material I shall present today, however, suggests that the problem is still vast, the ethically questionable experimentation widespread, and the mechanisms for systematic review little more effective than in 1966. I shall present a summary of the research designs of 12 studies selected from a collection of 43 questionable experiments. All have been published in reputable medical journals or presented at major professional meetings since 1966. In all cases the research was done in the United States or the funding came from this country.

Since my purpose is to raise the general problem of reviewing human experimentation and not to criticize specific researchers, I shall not refer to experimenters by name. The complete list of references has, however, been made available to the staff of the subcommittee to authenticate the tragic findings. I have excluded from these 12 all cases published before 1966 and those which have received public attention previously. Thus, I will not pursue several more widely known cases such as: the injection of live cancer cells into dying patients without their knowledge; the infection of mentally ill, institutionalized children with hepatitis; the withholding of penicillin from black patients affected with syphilis; and the substitution of placeboes for birth control pills at a clinic serving a population primarily of low-income Mexican American women, seven of whom became pregnant.

The tragic fact is that less than 25 percent of the studies in our file claim that consent was obtained from the participating subjects in the research, and not one paper documented the nature of the information given to subjects in conjunction with their consent. It is a very rare scientific article which explains the nature of the consent procedure, a deficiency which must be corrected.

Nevertheless, I have in no case taken the lack of consent as a criterion for inclusion in our set of articles. They must have raised more provocative ethical questions. It is impossible to say for sure that each of the studies I shall mention is an example of unethical research. Opinions may differ among even the disinterested and in any case a detailed study of each procedure would be required before any such claim could be made. I believe, though, that "reasonable men" would agree that each raises very disturbing questions and I, for one, would be willing to say that there are many ethical abuses among them.

GRAVE RISKS TO SUBJECTS

The first type of experiment which I identify as ethically questionable is the one which the subject is exposed to grave risks—risks which reasonable and informed persons might well refuse to take.

Experiment 1. Researchers in the first experiment to be cited were seeking a way to evaluate anti-arrhythmic drugs. In nine normal female patients epinephrine was injected at a rate of 4 g./minute. If arrhythmia was not produced, dosage was increased in 50 percent increments until the threshold for production of ventricular arrhythmia was ascertained.

In every case, the production of arrhythmia was repeated at least once. The researchers note that the production of arrhythmias experimentally had previously been avoided because of the belief that it was hazardous. They also tell the reader that although the procedure was explained to the subjects, they believe that "informed consent cannot be obtained for a study of this type." They claim that instead they "accepted the role of guarantor of the patient's rights and safety . . ." this while they were artificially inducing abnormal heart rhythms.

Experiment 2. In the second study researchers sought to study plasma renin levels in bilaterally nephrectomized patients—i.e. patients with both kidneys removed. Ten patients, who had had their kidneys removed as recently as two weeks prior to the experiment, were hospitalized for the eight-day period of the study.

A few days prior to the beginning of the study, they were transfused "in anticipation of blood loss due to repeated sampling." On the third day, "all subjects were clinically dehydrated. Serum samples were limited to the supine position since severe hypotension and near syncope rapidly developed in standing."

On one day measurements were taken after standing quietly for two hours. According to the researchers, "to accomplish two hours of quiet standing, it was necessary to have most of the patients lean on a chest-high supporting table and to be frequently encouraged."

Senator KENNEDY. What was the reason for the experiment?

Mr. VEATCH. It was a study to examine the renin levels in patients who had had kidneys removed.

Senator KENNEDY. For what purpose?

Dr. VEATCH. It is presumed that kidney function would change the renin levels in the blood.

Senator, I think you will have to be aware that I am not a physician; my field is medical ethics, so the technical questions regarding specifics of purpose are best referred to those who are medically trained.

Experiment 3. The third study we shall cite involved the giving of 200 ug of LSD to 24 male subjects who had answered an advertisement for experimental subjects to be paid at a rate of $2 per hour.

The purpose of this was to study the long-range "personality, attitude, value, interest, and performance change . . ." Additional "control" groups of 24 received amphetamine and 25 ug of LSD. The researchers claimed explicitly that no mention was made to subjects of possible personality or other changes although 15 percent reportedly had never heard of LSD and another 73 percent had "only casual knowledge" of it.

RISKS TO INCOMPETENT AND INCARCERATED SUBJECTS

Research involving risks to incompetent subjects—such as children and mental patients—brings even more serious ethical difficulties.

Experiment 4. In the fourth study, nine children from 11½ to 16 years of age suffering from asthma were intentionally subjected to "challenge doses" of antigens known to produce asthmatic attack in order to test the effectiveness of cromolyn sodium in blocking these attacks.

The nine children, were subjected to a total of 55 antigen challenges, 20 of which were preceded by treatment by cromolyn sodium.

Every child experienced at least one reaction described by the researcher as "severe." In addition, delayed asthmatic reactions six to 12 hours after the challenge were reported in five of the nine children. It is reported that these delayed reactions "tend to be followed by increased, and repeated asthma for a further day or two." Although seven of the nine children required regular bronchodilator medication, this was withheld for a period of 18 hours prior to the study.

Experiment 5. A fifth study also exposed children to risks. Forty-eight subjects ages seven to 12, with findings confirming or suggesting the presence of hematologic disease were subjected to simultaneous dualsite bone marrow aspirations in research designed to determine whether there are significant intra-individual variations in the cellular content of marrow obtained from two different body sites. Bone marrow samples were removed with an 18 gauge needle.

The researchers point out that there are "physical and psychological problems in performing multi-site, concomitant bone marrow aspirations in the pediartic patient."

Experiment 6. Similar ethical questions arise in research on mental patients and prisoners where the quality of consent, even if it is obtained, is questionable. At a maximum security facility for treating mentally disordered sex offenders, mentally ill patients, and the criminally insane, 90 male patients were "used in an exploratory study to determine the effectiveness of succinylcholine as an agent in behavior modification."

Succinylcholine causes temporary muscle paralysis including inability to breathe. During the period when breathing is impossible, positive and negative suggestions are made to the subject which, according to theories of psychological conditioning, are then associated with the experience.

The experience in this case is apparently not physically painful. It involves neither loss of consciousness nor memory, but the subjects describe the inability to breathe, which according to design lasts 1.25 and 2 minutes, as a terrible, frightful experience akin to that of drowning.

The criteria for selection of subjects for the study according to the researchers, included "persistent physical or physical or verbal violence, deviant sexual behavior, and lack of cooperation and involvement with the individual treatment program prescribed by the patient's ward team."

Experiment 7. A similar experiment in operant conditioning was reported by an American psychiatrist who at the time of the study was working at a mental hospital in Vietnam. The psychiatrist initiated a program in which 130 chronic patients were offered a chance to go home under the condition that they would have to work and support themselves.

As a trial they would have to prove themselves for a three-month work period in the hospital. Ten patients volunteered for work. The work offered including tending crops for American Special Forces—Green Berets—in Viet Cong territory "under the stress of potential or actual VC attack or ambush." The remaining 120 were told that those who were too sick to work must be treated. The "treatment" starting the next day was unmodified electronconvulsive shock.

Unmodified electroshock produces systemic convulsions similar to a grand mal epileptic seizure and in many patients is very terrifying. Although bone fractures may occur the researcher claims none were reported in his program. The test was repeated in a group of 130 women. When electroshock was found less persuasive to the women, withholding of food for periods of up to three days was used as a conditioning technique.

Senator KENNEDY. What is the research value of that?

Dr. VEATCH. The entire field of behavior conditioning is of great interest in the treatment of mental patients as well as prisoners, and avoidance conditioning, aversive conditioning of this type is of great interest to determine whether it will be effective.

I think there will be additional comments later in the hearings on this. It is of great interest, and a number of studies of this kind are going on now.

THE RIGHTS OF SUBJECTS IN RESEARCH WITH A PLACEBO GROUP

There is one class of experiments for which, even today, there are no clear guidelines. A well-designed experiment often requires a placebo group for purposes of comparison. The study in which women became pregnant when given placebo in place of a birth-control pill has been well publicized. Similar studies raise the same ethical problems.

Senator KENNEDY. Would you define "placebo"?

Dr. VEATCH. The giving of a sugar or salt solution pill, an ineffective drug, that appears to be the same as an effective drug.

Experiment 8. One such study was a 14-year prospective study of the value of hyposensitization therapy for children with bronchial asthma.

Of 130 children still under observation at the time of their 16th birthday, 91 received ineffective treatment for periods apparently lasting up to 14 years. This included a group who "received injections of buffered saline according to an elaborate 'injection schedule'," although the exact number in this group is not identified in the published research.

The authors point out that "No mother or child in the study knew that any sort of study was under way." Shocking as it may seem, no established principle of medical ethics requires that subjects be informed that one of the "risks" of an experimental procedure is that there is a placebo group included in the research design. While some researchers have felt morally obliged to follow this procedure, even the new rigorous HEW guidelines do not mention this specifically.

Senator KENNEDY. You mean in effect they were not getting anything at all? Of the 130 children, 91 were receiving placebos; is that correct?

Dr. VEATCH. Actually, Senator, the statistics in the published article are a bit vague. The 91 included a group who received a very small dose, a micro-dose, of the hypersensitization compound which they suspected would not work but were including as a reasonable clinical trial.

In addition to that, however, there was a group, the number of which was not indicated, who received only the saline, and that would certainly be no effective treatment. It was known in advance that that treatment would not be effective in that group.

Senator KENNEDY. Did the children understand that, or the parents?

Dr. VEATCH. The authors of the article state explicitly that neither the child nor the parent was informed that there was even a study going on, let alone that they were receiving in effect this medication.

Senator KENNEDY. They did not even know they were part of an experiment?

Dr. VEATCH. That is correct.

Senator KENNEDY. Neither the parent nor the child involved in that study had any idea they were getting either the placebo or the other drug to remedy the situation?

Dr. VEATCH. That is correct.

They also were not informed, which seems to me to be a reasonable requirement, that there was a placebo group in the design.

Obviously, one does not tell an individual that he is getting a placebo; it would spoil the study; but there is no reason to refrain from telling a person there is a placebo group in the study.

Senator KENNEDY. But they did not even understand that they were in a study at all?

Dr. VEATCH. That is correct.

Senator KENNEDY. As the father of an asthmatic child and as an uncle of a number of asthmatic children, I can well understand the enormous amount of time and personal attention needed for the child who is receiving the treatment—Marax, adrenalin, and all the rest.

As I understand, everybody involved in the treatment of asthma must understand the importance of making sure that the proper desensitization is carried out; so it is not only an outrageous situation with regard to the treatment of the children during a time of greatest need, but it also has an effect on the ability of the child to really overcome the disease as he grows up.

Dr. VEATCH. Yes.

We see no reason why this should not be one of the minimal requirements of informed consent.

Senator KENNEDY. Were the parents paying for this treatment?

Dr. VEATCH. This is not reported. There is no way for me to know for sure.

Senator KENNEDY. They must have been paying something. They would not just walk in if they did not know it was an experiment.

Dr. VEATCH. It is quite possible they were treated as clinic patients, however, and I am just not prepared to say. It is not in the published material.

Senator KENNEDY. If they were clinic patients, they would be either rich or poor?

Dr. VEATCH. That is right.

Senator KENNEDY. Which would they probably be?

Dr. VEATCH. Certainly they would be poor—although I have known rich people to attend clinics—for the most part they are poor.

Senator KENNEDY. Do you find many rich people who are involved in these kinds of experiments?

Dr. VEATCH. It is very rare, sir. I would advocate as a flat policy that at least half of the subjects of any research do not come from clinic populations. It seems to me to be the only way to protect the clinic population that is now obviously the major contributor of research subjects.

Likewise, the right of a patient to receive within a reasonable time any therapy found to be effective if he should have been included in the control group of an experiment should be recognized in those cases where such therapy could be meaningfully offered to patients. Such a right is not yet clearly established.

I think of cases where drugs for chronic treatment, such as Parkinson's disease, have been tested. It seems to me that generates an obligation to use the effective drug on the control patient.

RESPONSIBILITY FOR HARM TO SUBJECTS

Another principle which is not now recognized is that of the responsibility of the researcher, the researcher's institution, or the funding agency for harm done to subjects during the course of an experiment. Newly established Department of Health, Education, and Welfare guidelines do specify:

> The agreement, written or oral, entered into by the subject should include no exculpatory language through which the subject is made to waive, or to appear to waive, any of his legal rights, or to release the institution or its agents from liability for negligence.

Research not done under HEW guidelines does not even require this, and there are many examples of exculpatory contracts.

The guidelines do not require that the subject be informed of an institutional obligation for harm done to subjects and do not even make clear that any such obligation exists.

Senator KENNEDY. To whom can the harmed subject look for any kind of recourse?

Dr. VEATCH. At the moment, a very good lawyer, if he happens to have one.

In reality, it seems apparent that the typical subject may not even know he has been harmed by the research, let alone know how to pursue it through the legal system in our society.

Senator KENNEDY. He does not even know he is involved in an experiment, and then he gets harmed, and he does not really stand much of a chance to do very much about it, does he?

Dr. VEATCH. At the moment, that is the case.

Experiment 9.—One clinical trial raising the question of the obligation for harm done involved 2,932 women from five clinics and one physician's private practice. The majority of these women were medically indigent. According to the researcher, the women "agreed to use vaginal foam as their only method of contraception while they participated in this investigation." Vaginal contraceptive foam is well known to be a particularly unreliable method of birth control. The present study tested a newly developed dispenser. The results included 94 pregnancies or a pregnancy rate of 3.98 per hundred women years of exposure.

Experiment 10. An experiment raising similar questions was conducted on Latin American women in a study supported by an American funding agency. In this study megestrol acetate capsules 20 mm. in length were implanted in a single implant under the skin of the forearm to test the effectiveness of this drug as a long-term contraceptive implant. In the group of 262 women, 48 pregnancies resulted including six which were ectopic.

We have in our files published reports of hundreds of similar experimental pregnancies.

To my knowledge, no researcher, including the experimenters in the famous San Antonio experiment, has ever accepted responsibility for the harm done in the form of an unwanted pregnancy.

A thorough search would certainly produce hundreds and perhaps thousands more. These studies together with other published and unpublished reports of harm done during experimental tests raise the question of the researcher's obligation. We propose for consideration that as a matter of policy the funding agency or highest level of institutional sponsorship be clearly obligated for such consequences of research and that this be clearly made known to subjects of research during the consent procedure.

Experiment 11. Another study may not have involved physical harm to patients, but may well have subjected them to legal and psychological risks without their consent. Researchers at an open-ward voluntary psychiatric hospital were interested in the extent to which young patients were engaged in covert drug abuse. In 332 patients serial urine analyses were performed weekly for an average of 27 weeks "under the guise of a statistical survey of urinary creatinine." The researchers state that "the urine analytic data were kept completely secret from all other members of the staff, and at no time were the patients or staff"—and that includes the physicians caring for these patients—"aware that the urine samples were being monitored for abusable drugs." This research was supported by, in part, a grant from the National Institute of Mental Health.

Experiment 12. The highly publicized experiments involving human subjects may give the erroneous impression that such procedures raising ethical questions are rare and involve only bizarre procedures. A final study indicates that this is not the case.

In this research, presented at a professional meeting, 41,119 patients enrolled in a major group health plan were given a test for pain tolerance as part of their regular checkup. The subjects were told it was a test for "pressure tolerance." Each subject placed his heel in a vise-like machine and was instructed to stand the pressure as long as he could. Researchers then compared age, sex, and racial differences in pain tolerance.

This is a relatively simple procedure. Similar simple tests are conducted in clinical settings, at times without formal review.

Senator KENNEDY. What would you do with that knowledge?

Dr. VEATCH. The researchers in their first paper on this made observations about racial, ethnic, sex differences in the pain threshold. They were able to observe, for instance, that one sex had a higher pain threshold than the other sex.

Senator KENNEDY. Do not tell me which one.

[Laughter.]

Dr. VEATCH. It is, I suppose, of scientific and academic interest. The point is that this was done by a reputable major group health provider as part of a checkup for 41,000 patients, which was an incredibly large sample.

Although the pain was not severe, and we may write it off, it is the kind of thing that can be done on a very massive scale.

In some cases, experimenters may not even conceive of what they are doing as an experiment. The problem, then, is one of developing mechanisms for consent and review which give greater assurance to the subject that his right and interests will be protected.

These experiments strongly suggest that the mechanisms now available are inadequate to the problem. The typical researcher may well be benevolently motivated and indeed do a good job of getting reasonably informed consent from his subject and protecting the subject's interests. That simply is not good enough, however. That experiments such as those described here can be performed and be published within the last few years means that we simply must intervene to guard the welfare of the citizens.

We can no longer tolerate a situation in which a citizen, altruistically motivated to participate in research, may be subjected to grave and undisclosed risks.

The immediate establishment of a governmental committee to formulate rigorous procedures to insure reasonably informed consent and review is the minimum that is called for. This might well be one of the functions of the proposed National Advisory Commission on Health Science and Society. Even more effective would be a special committee with this as its sole task. The committee should include a substantial majority of individuals who are in no way associated with biomedical research.

The first priority of this committee ought to be the refinement of consent procedures discussed above, including the requiring of information on (1) the possibility of receiving placeboes, (2) institutional responsibility for harm done, and (3) commitment to provide effective therapy to members of control groups. This committee ought to develop procedures requiring such informed consent from all subjects or their guardians—not simply those falling under HEW guidelines.

The committee ought also to develop new mechanisms for research review. One of the great problems of peer review as we know it today is that even when it is used in a serious way—which happens all too rarely—it is the peers of the researchers and not the peers of the subjects who are asked to evaluate the ethical acceptability of the proposed research.

It is simply too much to ask individuals uniquely committed to the importance of medical research to judge the ethical acceptability of their colleagues' work in a disinterested manner. New and more public mechanisms are needed to assure subjects that their ethical and legal rights will not be violated by the minority of researchers who are misguided or irresponsible in their judgment of a person's welfare.

I would be happy to answer questions.

Senator KENNEDY. How many of the medical schools have faculty members who are well versed in medical ethics?

Dr. VEATCH. As part of a program in medical ethics at the Institute of Society, Ethics and the Life Sciences, I have conducted a survey of all the medical schools regarding medical ethics teaching.

It is very difficult to define what medical ethics is; but I would say that figuring generously, there are 15 schools who have at least a half-time person who would identify as a medical ethicist. Certainly not more than that.

Senator KENNEDY. What kind of education do young medical students receive in this?

Dr. VEATCH. We have also attempted to establish this in the survey. If you ask any given dean of a medical school, he will say there is some place where medical ethics is taught. They may have talked about it one night during the first year, or something to that effect.

There are approximately 30 schools that offer an elective course in medical ethics taken by various members of medical students.

There are no more than eight schools that have a normal program to be called a medical ethics program.

Senator KENNEDY. Do you remember what they are?

Dr. VEATCH. What the schools are?

Senator KENNEDY. Yes.

Dr. VEATCH. They would include the experimental program at Harvard, the program at Georgetown, which is affiliated with the medical school, and where courses are also offered.

There is an experimental teaching program at Case Western Reserve. Our institute jointly sponsored a program at the Columbia College of Physicians and Surgeons. The Medical College of Georgia has a two-man faculty. Penn State at Hershey has a Humanities Department as does the State University of New York at Stonybrook.

I think that summarizes the major efforts.

Senator, I would emphasize that even in these schools where there is a conscious and systematic effort, I am not convinced that medical ethics teaching is the answer to stopping the kind of experimentation which is taking place by a minority of individuals, even if there is the best quality medical education in this area.

Senator KENNEDY. Do you think there are any circumstances at all in which a patient ought to be included in experiments, in studies, and not know he is in fact enrolled in such a study?

Dr. VEATCH. In the case of a competent and conscious patient, I can conceive of no such study.

In the case of patients needing therapeutic treatment, which may be experimental, who would be either children or perhaps comatose patients, I can conceive of cases where adequate consent from a legal guardian would be acceptable. We may have to bring young children into an experimental procedure for therapeutic purposes.

Senator KENNEDY. How did some of these experiments get through the institutional review committees? Do not most of the university centers have those?

Dr. VEATCH. I think it is fair to say that most centers have some sort of review. Dr. Barber has the best and most up-to-date data on that. Perhaps that could be asked him.

However, many of these studies were not done in a university or major teaching hospital setting at all. Some of them were funded by drug companies, done in private research centers, and even in the case where there is an institutional review, I am very pessimistic about the quality of review that goes on.

After all, the review procedure involves the asking friends and long-term colleagues to give a vote of approval. I participated in one such review, and it came to the point of asking, "Well, shall we let John do his research?" As old friends, it is very difficult to provide disinterested and critical review of the study.

Senator KENNEDY. What are you going to do about that?

Dr. VEATCH. I am hoping that a committee such as the one that I have suggested would give these problems thorough examination. I think the value of the peer review procedure has been greatly over emphasized. We need review mechanisms that are not dependent upon institutional peer review as the sole mechanism of reviewing the ethics of research being proposed.

Certainly the scientific merits of scientific proposals might be effectively reviewed by one's colleagues, even though then I have some doubt about the objectivity of the review, but there is no reason one's peers in a local institution are either qualified or disinterested in the review of the ethical and social implications of the research.

Senator KENNEDY. What are the remedies available to people who are involved in these experiments and are harmed by them?

Dr. VEATCH. At the moment, as I indicated before, unless there is goodwill and one happens to know that he has been harmed and appeals to the goodness of the researcher, the only mechanism is the traditional legal suit, which requires, first of all, knowledge of the system and access to a lawyer.

Senator KENNEDY. That is not very much.

Dr. VEATCH. It is not very much, particularly for a group of patients who tend to be subjects, who are not often well acquainted with either lawyers or legal procedures.

We are also harmed here by the well-recognized principle of medical ethics, that the researcher will not release the identity, the names of his subjects. So even though we know a subject is harmed, we cannot always get to him to provide legal counsel.

Senator KENNEDY. Senator Javits would be interested in your recommendations to overcome research problems which you have indicated in your testimony. Much of his bill, S. 78, is addressed to the placebo and information concerning obligation for harm.

Maybe you can submit something on that to him.

Dr. VEATCH. Yes. I am familiar with last year's proposal. I do not know how this year's relates to it.

One problem, at least with last year's bill, was that it still limited control to only federally funded research. There is a great deal that goes on that is not funded through Federal mechanisms.

Senator KENNEDY. Thank you very much.

At this time I order printed in the record all pertinent material submitted in conjunction with this hearing.

[The following was subsequently supplied for the record:]

ADVERSE REACTIONS AND DRUG INTERACTION

A critical analysis of the Talley paper

February 20, 1973

The subject of adverse drug reactions has recently received national attention as a result of two articles, by Morton Mintz of the *Washington Post* and Judith Randall of the *Washington Star*. The stories were based on a press release issued December 17 from the office of Senator Edward M. Kennedy (D-Mass.).

The release publicizes the findings of a recent study entitled "Drug Utilization and Peer Review in San Joaquin," by Robert B. Talley, M.D., and Mark F. Laventurier. It includes a number of alarming items, most of which are in conflict with information available from other sources. These items cover two subjects: (1) Data on adverse effects, (2) Comments on drug interactions.

ADVERSE EFFECTS

Talley and Laventurier	This report
(1) Adverse drug reactions are reported to occur in about 15 per cent of all patients in a medical service.[1]	(1) Adverse drug reactions are reported to occur in about 15 per cent of all patients in a medical service, and in about 6 per cent of patients in an entire hospital.[2] Other studies suggest considerably lower rates.[3]
(2) An adverse drug reaction increases the length of hospitalization, on the average, by about 100 per cent.[4]	(2) An adverse drug reaction increases the length of hospitalization, on the average, by about 20 per cent.[5]
(3) About 80 per cent of adverse drug reactions may be preventable.[6]	(3) About 20 per cent of adverse drug reactions may be preventable.[7]

(4) Costs of hospitalization may be estimated at $90 per day.	(4) Costs of hospitalization may be estimated at $90 per day.
(5) Therefore, a large sum of money (unspecified, of the order of $1 billion) may be saved in hospital costs alone by proper utilization and control.[8]	(5) Therefore, about $50 million may be saved in hospital costs alone by proper utilization and control.[8]
(6) Modern therapeutic agents have created the "formidable health problem" of drug reactions. New drug introduction worsens the adverse reaction rate.[7]	(6) Over half of all adverse reactions are caused by "old" drugs such as digoxin and quinidine. New drug development improves the adverse reaction rate.[7]
(7) Adverse reactions account for 4 to 7 per cent, or about 5 per cent, of all hospital admission.[9]	(7) Adverse reactions account for 0.1 to 1.3 per cent, or about 0.5 per cent, of all hospital admissions.[9]
(8) There are approximately 1.5 million hospital admissions per year due to adverse drug reactions.[10]	(8) There are at the most 150,000 hospital admissions per year due to drug reactions, or much less.[10]
(9) Thus 12 million patient days are directly attributable to adverse drug reactions for which patients are admitted.	(9) Thus 1.2 million patient days are directly attributable to adverse drug reactions for which patients are admitted.
(10) $1.1 billion in hospitalization costs are directly attributable to adverse drug reactions for which patients were admitted.	(10) $110 million in hospitalization costs are directly attributable to adverse drug reactions for which patients were admitted.

(11) 80 per cent, or $880 million, may be preventable by proper usage.[10]	(11) 20 per cent, or $22 million, may be preventable by proper usage.[10]
(12) Summing items (5) and (10), a grand total of $1.2 to 1.8 billion can conservatively be saved in hospital costs alone by proper drug utilization and control.	(12) Summing items (5) and (10), a grand total of $72 million annually can possibly be saved in hospital costs alone by proper drug utilization and control.
(13) Deaths from adverse drug reactions are about 30,000 a year.[11]	(13) Deaths from adverse drug reactions are about 20,000 a at most, or much less.[11]
(14) 80 per cent of these, or 24,000 deaths per year, may be preventable.	(14) 20 per cent of these, or 4,000 deaths per year, may be preventable.
(15) One in four adverse drug reactions results from undesirable drug interaction.[12]	(15) One in 40 adverse drug reactions results from undesirable drug interaction.[13, 14]
(16) Deaths from undesirable drug interactions may be estimated at 7,500 per year.	(16) Deaths from undesirable drug interactions may be estimated at 500 per year.

DRUG INTERACTION

The figures, it seems, are grossly exaggerated. This is unfortunate, for even 500 deaths a year from drug interaction are 500 deaths too many, and by this carelessness the real message of drug interaction studies and of the Talley-Laventurier paper may be lost.

For one thing, there is no evidence in their study to prop up the fearful figures cited above. There are in it no data on adverse reactions du drug interactions. Dr. Talley and Mr. Laventurier explicitly note: "At this time, no attempt has been made to determine the clinical significance of these potential interactions."[15]

Furthermore, the press release from the office of Senator Kennedy starts with the statement: "Thousands of people die and hundreds of thousands more are hospitalized each year as a result of adverse drug reactions... One quarter of these adverse drug reactions are caused by the patient being told to take 2 drugs that should not be taken together. This deeply disturbing situation was brought to my attention by a recent study... by Robert B. Talley and Marc Laventurier."

This wording gives the impression that Talley and Laventurier have made the following discovery: Many drugs (a) are being given together, which (b) are incompatible. Both parts of this statement are incorrect: (a) Talley counted drugs which were taken up to 60 days apart -- if you got a salicylate two months ago and an anticoagulant today, then you were counted as getting them together.[16] (b) There is nothing incompatible about the drugs he studied; a physician who properly prescribes an anticoagulant and a salicylate at the same time keeps in mind the effect of the two drugs on each other and adjusts the dose accordingly.[17]

The wide dissemination of these errors is harmful. Without justification, such exaggerations scare the patient and libel the physician.[18] And they distract attention from the potential public health import of this new work.

Dr. Talley and Mr. Laventurier should now turn from printouts to physicians. They may then find out whether these potentially interacting drugs were properly or improperly prescribed, and whether there were more adverse reactions in these cases. The resulting findings will be less newsworthy, but more helpful. In this fashion, their work can yet lead to an actual improvement in prescription practices.

If drug interactions represent a significant public health problem, then there will be increasing need for new drug research and development. Older drugs seem to have an increased adverse reaction potential,[7] and to lock the physician into therapeutic situations where few or no other medicinal options are open to him. Advances in drug technology may aid in solving the problem of drug interactions and reactions, by providing equivalent alternative therapies without the potential to interact.

Finally, it should be emphasized that the figures on incidence of adverse drug reactions cited by Talley and Laventurier, and the figures cited in this report, are all based on extrapolations. The knowledge base for accurate estimates in this field has not as yet been developed, and further work may show that all these extrapolations lead to grossly excessive ideas of the morbidity and mortality from side effects.

FOOTNOTES

(1) Incidence of ADR (adverse drug reactions) on medical wards: The reports of this rate vary widely. The highest incidence of adverse drug reactions, 35 per cent, is reported by Borda et al (1968). However, only 70 per cent of these were thought "definitely" or "probably" due to the drug implicated, so that the confirmed ADR rate falls to 24 per cent. Borda et al, working at the Lemuel Shattuck Hospital, Boston, state that this high figure "may partly be due to the collecting system, but the relatively long hospitalization, the chronic illness of these patients, the multiplicity of drugs used, and the careful surveillance of patients could also be responsible for the observed higher incidence." Later, Slone et al (1969), again studying the medical wards of the Lemuel Shattuck Hospital, reported an ADR rate of 31 per cent.

Other reports include those of Bergman et al, Veterans Administration Hospital, Iowa City (1971) (21 per cent); Ogilvie et al (1967), Montreal General Hospital (18 per cent); Simmons et al (1968), University of Western Ontario (18 per cent); Hurwitz and Wade (1969), Belfast City Hospital (16 per cent, medical wards only); Hoddinott et al (1967), University of Western Ontario (15 per cent, plus 16 per cent medication errors, mostly omission of a prescribed drug); Schimmel (1964), Grace-New Haven Community Hospital (10 per cent, plus 10 per cent non-drug noxious episodes such as transfusion reactions).

The most widely cited study of adverse reactions is that of Seidl, Thornton and Cluff (1965). On the medical service of the Johns Hopkins Hospital, they report that "patients are given many drugs when hospitalized, and at least 15 per cent develop adverse reactions, ranging from incidental to fatal ones." A later report from the same group (Smith 1966) shows an incidence rate of 11 per cent, because the investigators decided to exclude mild reactions (nausea, diarrhea) which may not be due to drugs at all. However, the earlier figure of 15 per cent has received considerable currency, and it may be considered valid at this time.

(2) High-risk wards: When a patient enters a hospital, he may be directed to the medical ward if he is under the care of a specialist in internal medicine, to the surgical ward if he requires surgery, and so on. Potent drugs will be used much more frequently on a medical ward, where they constitute the main method of treatment, than elsewhere. The ADR rate will therefore also be highest on the medical ward. It is as wrong to say that 15 per cent of patients admitted to hospital are likely to have an adverse reaction to drugs, as it is to say that 100 per cent of patients are likely to be pregnant -- both are true only on the medical and the obstetrical wards, respectively.

As Reidenberg (1968R) notes, the population of the entire hospital includes both a population at "high risk" for adverse drug reactions, the patients on medical services who are sick and often receive many medications; and "low risk" groups such as healthy postpartum women and elective surgery patients. And Seidl et al (1965) point out that on a medical service, particularly during the first few days, "the patient is usually acutely ill, subject to the intensive diagnostic and therapeutic endeavors of the staff -- and at risk to more procedures and drugs given simultaneously."

The actual incidence of adverse effects on different wards has been studied by Hurwitz and Wade (1969). They obtained figures of 16 per cent for medical, 8 per cent for dermatological, 3 per cent for surgical, and 2 per cent for psychiatric wards. At the Johns Hopkins Hospital, there are about 32,700 admissions per year, of which 6,700 (20 per cent) are to the medical ward. Most of the other admissions are for surgery or the various surgical specialties. If we assign an average reaction rate of 15 per cent to the medical and 4 per cent to the other wards, we arrive at an over-all adverse reaction rate of about 6 per cent.

The low incidence of ADR's on surgical wards is not due to under-reporting. More surgeons than internists have been found to make "false-positive" adverse reaction reports (Koch-Weser 1969), i.e. they tend to over-report rather than under-report.

(3) Low rates of adverse reactions: Only two large-scale studies of entire hospitals are available, and both are retrospective studies, i.e. studies in which patients are not examined daily to find out if they have an adverse reaction, but in which reports of adverse drug reactions are received from physicians.

First, MacDonald and MacKay (1964), Mary Fletcher Hospital, Burlington, found 98 reactions for 9,600 admissions, or about 1 per cent. The second study was reported by the Drug Reactions Registry Subcommittee of the Greater Philadelphia Committee for Medical Pharmaceutical Science (Reidenberg 1968R). They reviewed reports of adverse reactions in the five medical school hospitals in Philadelphia for a period of two years. There were 772 reactions for 172,200 admissions, or about 0.5 per cent.

With prospective studies yielding a 6 per cent rate, and retrospective studies about a tenth as much, the true value of the adverse reaction rate is likely to lie between these two. A value of about 0.5 per cent is likely to be 3 times too low because of under-reporting (Sidel 1967). A value of 6 per cent is likely to be 2 times too high because of the fact that people not taking drugs are likely to report symptoms just like those of side effects (Reidenberg 1968A)(Editorial 1969). As Gardner and Cluff (1970) show, "a legitimate criticism of the epidemiological studies reported to date is the absence of adequate control data showing the incidence of manifestations of illness similar to those caused by drugs but occurring in patients not receiving drugs."

It can be predicted, therefore, that when ADR studies are done with the proper safeguards, the true level of adverse reactions will be found between 2 and 3 per cent of hospital admissions. Proper safeguards include: (a) Prospective and not retrospective study; (b) Entire hospital and not selected wards; (c) Subtraction of incidence of "adverse reactions" in patients not receiving drugs (control group).

(4) Doubling of hospital stay: Talley (1972D) speaks of "the prolonged hospital stays which have been documented as being doubled," but gives no documentation on this point. Gardner and Cluff (1970) state that "a detailed cost analysis of the morbidity due to adverse drug reactions has not been published, but it seems clear that the effect on hospital expenses is significant."

Melmon (1971) states that the use of modern therapeutic agents "has also created a formidable health problem: 18 to 30 per cent of all hospitalized patients have a drug reaction, and the duration of their hospitalization is about doubled as a consequence." The first half of this statement is inflated by a factor of 5, as we have just seen. In the second half, the doubling of hospital time, Melmon cites Seidl et al (1966S), Hoddinott et al (1967), Schimmel (1964), and Ogilvie and Ruedy (1967). These citations are inaccurate.

Seidl et al report that the average duration of hospital stay was 21 days for patients with, and 14 days for patients without ADR. But nowhere do they indicate that this prolonged stay is in consequence of the ADR; on the contrary, they indicate elsewhere that in only one-half the reactions was there need to prolong hospitalization by at least one day.

The paper by Hoddinott et al sounds as if, in 1967, they had been aware that four years later Melmon would misinterpret their findings by saying that hospitalization is increased as a consequence of drug reactions. They state:

"In the present study, patients who suffered reactions were observed in hospital for a period of about 50 per cent longer than the average hospital stay of all patients. In retrospect, we perhaps should have asked the doctors whether they believed that the reaction prolonged the patients' stay. This was not done and one can only speculate that (a) the reaction may have prolonged the stay, or (b) the patients may have stayed longer for other reasons and were thus exposed for a longer period, or (c) their observation period was longer and thus there was more chance of observing a reaction. The fact that patients involved in errors were observed as long as those with reactions (20.4 and 20.8 days, respectively) suggests that the length of the observation period is the main factor leading to the detection of these reactions.

The reports by Schimmel and by Ogilvie are discussed below.

(5) Lengthening of hospital stay: The hospital stay of patients with ADR's is longer than that of patients without, but it is not the adverse effect which leads to the longer stay; on the contrary, the longer stay leads to the adverse effect.

Ogilvie and Ruedy (1967), for example, find that patients who experienced ADR during hospitalization stayed 21 days, while all other patients averaged 12 days. The authors state, however, that adverse reactions may not have caused this prolonged stay, but rather that the patients susceptible to drug reaction were also patients requiring longer hospitalization. Similarly, Schimmel (1964) reports:

"Patients encountering noxious episodes had a mean total hospitalization of 28.7 days, compared with 11.4 days in other patients. The risk of having such episodes seems directly related to the length of time spent in the hospital."

But how much of this prolonged stay may be attributed to the reaction itself? This can be determined by observing, for each patient with ADR, how much additional hospitalization was caused by the reaction. The answers to such surveys vary. Hurwitz (1969P) reports that patients with adverse reactions did not stay in hospital significantly longer. Borda et al (1968) state that 12 per cent of reactions led to prolonged hospitalization, and an unpublished study by Gardner and Watson (Gardner 1970) indicates that 48 per cent of patients experiencing reactions had their stay extended for this reason. Neither of these reports tells us by how long the stay was prolonged.

In the absence of more detailed data, it seems clear that the average prolongation of hospital stay in these various groups is less than 50 per cent, and more than zero. The figure of 20 per cent may be used as a tentative estimate.

(6) Preventable drug reactions: Talley (1972D) uses a factor of 80 per cent preventable drug reactions in his calculations. In support, he cites Melmon (1971) as having claimed that "70-80% of these reactions are both predictable and preventable." Actually, Melmon's opinion is that "classic reactions take up less than 20 to 30 per cent of drug reactions; the remaining 70-80 per cent are predictable. Most of these are preventable without compromise of the therapeutic benefits of the drug." Melmon is opposed to our being a pill-taking society ("a major cause of preventable drug reactions is that too many pills are prescribed"); but in spite of this bias, his figure of preventable reactions seems closer to 50 than to 80 per cent.

(7) Inevitable drug reactions and the role of older drugs: There is no question but that some adverse effects of drugs are preventable, and that it is the duty of both planning and practicing physicians to do all in their power to lower the resulting toll. But under the most favorable circumstances, what reduction of side effects is likely to be achieved?

Seidl et al (1966S) conclude, from their extensive study at the Johns Hopkins Hospital: "Some deaths and life threatening reactions to drugs could have been prevented if greater attention were given to proper notation of reactions patients had had previously. The increased rate of adverse reactions in patients who previously have had one even to different drugs, indicates the importance of personal factors influencing predisposition." No detailed figures on this are given, and it may be estimated from other data (Stewart 1971) that such a situation might have preceded 10-20 per cent of adverse reactions.

Ogilvie and Ruedy (1967) ask: "Whether or not these untoward events can be prevented is the most critical question. Are the reactions predictable or are they for the most part unusual and unexpected reactions?" They reply that about 80 per cent of the reactions in their study were pharmacologic and predictable, and that physician care in the use of drugs should eliminate many (not most) of these reactions. It may therefore be concluded that, in their estimate, about 30 per cent of adverse reactions are preventable.

The Philadelphia Drug Reaction Registry Subcommittee (Reidenberg 1968R), on the other hand, found that 65 per cent of ADR's consisted of allergic or skin reactions, effects which cannot be termed pharmacologic or predictable. If we now assume that, at best, half of all other reactions are preventable, we obtain a figure of about 20 per cent.

. Witts (1965), describing the work of his British Subcommittee on Adverse Reactions, strongly contradicts the view that most side effects are preventable. Discussing reports of unfavorable drug effects in 15-20 per cent of patients admitted to medical wards in the U.S., he states: "Most of these unfavourable effects, however, are of a type on which our committee would not expect reports. They are phenomena such as the side-effects of corticosteroids or symptoms of overdosage of anticoagulants or allergic reactions to penicillin, which are already well known and some of which are inevitable when powerful drugs are used and optimal doses are being worked out."

Another factor interfering with prevention of adverse effects by physicians is the reportedly heavy incidence of self-medication and drug misuse. Stewart and Cluff (1972) note that the percentage of patients making errors in the taking of prescribed drugs has been said to range between 25 and 60 per cent; that 4 to 35 per cent of patients misuse their medications in such a manner as to pose serious threats to health; and that in their own study a high percentage of patients are admitted to the medical service with adverse drug reactions resulting, not from the inherent toxic property or an idiosyncratic reaction, but from improper use of the drug. In addition, Stewart and Cluff (1971) found that 43 per cent of prescription users were taking drugs from multiple prescribers, some from as many as four.

Melmon (1971) suggests that it is modern therapeutic agents which, in spite of their advantages, have created the "formidable health problem" of preventable drug reactions. On the contrary, most of the drugs implicated in the more serious adverse reactions are "old" -- such as cardiac glycosides, insulin etc. -- for which new, good alternative therapies may not exist. Ogilvie and Ruedy (1967) emphasize this point:

"It is remarkable that 38% of all adverse drug reactions in our patients were due to three agents which have been used in medical practice for over 30 years -- digoxin, quinidine and insulin. If reactions to other drugs such as acetylsalicylic acid, phenobarbital, paraldehyde, adrenalin, heparin, thyroid extract and purgatives are added, the percentage of reactions caused by these 'old' drugs was over 50%. The majority of remaining reactions was due to drugs which have been in use for more than 10 years. It cannot be said that the high incidence of reactions was due to new drugs with which the medical profession has had little experience. Four drugs or drug groups -- digitalis and quinidine, antimicrobials, insulin and diuretics -- caused 60% of reactions."

It is clear, therefore, that with most adverse reactions, we are not dealing with new, surprising, or unexpected effects, or with freshly discovered interactions, but with regrettably well known properties of the drugs in question. No amount of peer review, monitoring or publicity is likely to be of as much help as the development of new technologies in pharmaceutical medicine: Newer and more easily controlled therapeutic agents; better methods of standardizing bioavailability; and more sensitive means of gauging or predicting patient response.

(8) Cost of preventable adverse reactions: The dollar cost ascribed to this type of preventable adverse reaction by Talley and Laventurier is not clearly stated. They estimate that up to $1.8 billion may be saved, and that $0.9 of this is allocated to preventable hospital admissions due to ADR's. It therefore seems that another $0.9 billion is incurred by way of preventable ADR's occurring within hospitals.

Actually, using their own assumptions, Talley and Laventurier might have indicated that the possible saving is of the order of $2.7 billion, as the table below indicates; or even more, since they use the low figure of $90 hospitalization cost per day. In the table, yearly admissions are taken as roughly 30 million, and average hospital stay as 8 days (Brown 1971).

	Talley	This report
Admissions (per year)	30,000,000	30,000,000
Adverse effects	4,500,000	1,800,000
Prolongation of stay (days)	36,000,000	3,600,000
Preventable (days)	30,000,000	700,000
Cost ($)	2,700,000,000	50,000,000

(9) Admission for reason of adverse drug reaction: Talley and Laventurier cite the National Center for Health Research and Development of HEW as estimating that there are approximately 1.5 million hospital admissions due to ADR's annually. This estimate is not referenced, but Sigell and Flass (1970) have stated that "Cluff's data from the Johns Hopkins Hospital projected nationally suggests that there are 1.5 million hospital admissions in the United States every year due to disorders caused by drugs."

This refers to the study of Seidl, Thornton, and Cluff (1965), in which they state that "it appears that about 5 per cent of all admissions to the public medical service were directly caused by drug reactions..." Since about 20 per cent of admissions are to the medical service (see note 2 above), and since drug reactions are not likely to be admitted to surgery or obstetrics, we can estimate that in the study of Seidl et al, 1 per cent of all admissions to Johns Hopkins Hospital were thought to be due to drug reactions.

In a later study from the Johns Hopkins Hospital group, however, 15 of 900 admissions to a medical ward (1.7 per cent) were "admitted specifically because of a reaction." This would indicate a rate of less than 0.5 per cent for the entire hospital.

Similar data may be obtained from the study of Hurwitz (1969A), specifically devoted to admissions to hospitals due to drugs. Among 1,268 admissions, there were 27 due to self-poisoning, 6 because of taking a drug in excess of the dosage prescribed, 19 because of adverse reactions to drugs which were thought to be the entire reason for the admission, and 12 because of adverse reactions to drugs which were an important factor in the admission. Taking the last two together, we have ADR's as cause of admission in 2.4 per cent of patients studied; and, correcting for the excess of medical wards in this study (see note 2), we arrive at a rate of 1.2 per cent for the whole hospital.

Ogilvie and Ruedy (1967) report an incidence of 6.5 per cent of admissions to a public medical service of patients with (not necessarily due to) an adverse effect. This would suggest that about 1.3 per cent of admissions to the entire hospital fall into this class.

A much lower incidence of adverse reactions due to drugs or household chemicals taken by patients prior to admission is reported by the Philadelphia Drug Reaction Registration Subcommittee (Reidenberg 1968R) -- 73 of 172,200 admissions, or 0.02 per cent. This study, compared to the others cited, has the disadvantage of being retrospective, and the advantage of covering 5 entire hospitals, not just selected areas of one hospital. Applying the correction factor for under-reporting in retrospective studies (see note 3), we arrive at an estimate of about 0.1 per cent.

These varying figures are hard to combine; but since the Johns Hopkins study was originally the trigger for the alarming figures cited by Talley, we may well take their corrected figure of 0.5 per cent of all hospital admissions, or 150,000 for the entire country.

(10) Small vs. large savings estimates:

The calculations leading to items (7) through (10) are tabulated below --

	Talley	This report
Adverse reactions as % of hospital admissions	5.0	0.5
Hospital admissions per year in U.S.	30,000,000	30,000,000
Hospital admissions due to ADR's	1,500,000	150,000
Average hospital stay (days)	8	8
Hospital days due to ADR admissions	12,000,000	1,200,000
Cost per day of hospitalization ($)	90	90
Hospital costs due to ADR admissions	1,100,000,000	110,000,000
Per cent preventable (from item 3)	80	20
Hospital costs preventable by proper usage	880,000,000	22,000,000

(11) Deaths from adverse drug reactions: Talley and Laventurier (1972D) cite an unpublished estimate by Silverman that deaths from ADR's are in the range of 30,000 per year, or approximately the same mortality rate as cancer of the breast. No documentation for this estimate is provided.

A prospective study of medical inpatients at six different cooperating hospitals (Shapiro 1971) shows that in a series of 6,200 consecutively monitored patients, deaths due to drugs administered in hospital were recorded in 27 cases (0.44 per cent). Applying the 0.2 correction to obtain a value for all hospital patients (patients were transferred to medical from other areas), we obtain a fatality rate of 0.1 per cent.

For an annual admission rate of 30 million, this gives about 30,000 deaths a year, equal to the estimate cited by Talley and Laventurier. But 9 of the 27 cases reported by Shapiro et al represent fatal reactions to fluid and electrolyte therapy. These are customarily classed not with drugs, but with hospital procedures such as transfusions (Gardner 1970)(Hurwitz 1969I)(Schimmel 1964). The estimate should therefore be reduced by one-third, to give 20,000 deaths from adverse drug reactions per year.

Since this figure is based on a single study in central medical locations, other studies must be awaited to gain a better view of the mortality caused by adverse reactions. High-risk patients may be preferentially drawn to such centers than to less prestigious facilities. Furthermore, yearly deaths ascribed to therapeutic misadventure were 160 in 1949 and 840 in 1958 (Sheps 1962). It seems hard to see how, in 14 years, the death rate could have gone up so far and so fast.

(12) High estimate for drug interactions: Talley and Laventurier (1972D) state, without documentation, that one fourth of all adverse drug reactions result from drug interactions (their study was not designed to elicit any figures on adverse reactions). This figure is, in part, supported by the group of pharmacologists at the Lemuel Shattuck Hospital, Boston (Borda 1968)(Slone 1969), who indicate that in 22 per cent of patients with possible adverse reactions, drug interaction was thought to have played a role (but not necessarily to have resulted in the side effect).

(13) Low estimate for drug interactions: It is difficult to decide whether a reaction is due to a drug interaction or not. Even after intensive study, the exact role of drug combinations in causing reactions is unclear (Smith 1966). And Puckett and Visconti (1971) state that their results "suggest that drug-drug interaction may not be the large problem in hospitalized patients that many authors have purported."

Puckett and Visconti, Grant Hospital, Columbus, screened 2,422 patients for potential drug interactions: 113 patients were found to have received potentially interacting combinations. Only 3 of these were considered to have interactions of minor clinical significance; none were of major significance. If these patients had the expected 6 per cent rate of adverse reactions (145 patients), then only 2 per cent of ADR's resulted from undesirable drug interaction, and only the milder ones at that.

Ogilvie and Ruedy (1967), Montreal General Hospital, carefully distinguished among different causes of adverse drug reactions. They found that 1.6 per cent were "drug-induced," defined as the result of interactions of drugs producing an unusual effect.

Bergman et al (1971), Veterans Administration Hospital, Iowa City, tabulated 113 admissions to a medical ward. There were 24 suspected adverse drug reactions, and 3.6 per cent of these were thought due to drug interaction.

Combining these results, we may arrive at the conclusion that, at most, about 2.5 per cent of ADR's result from undesirable drug interaction. But how does this mesh with the about 10 times greater incidence reported by the Lemuel Shattuck group?

(14) Polypharmacy and adverse effects: The clue to the disagreement is provided by Slone et al (1969), who state:

"In 22 per cent of the patients with possible side effects, drug interaction was thought to have played a role. This result supports the hypothesis that multiple drug treatment increases the likelihood of side effects."

It seems, therefore, that Slone et al have been guided to their conclusions by the well-established fact that the patient who gets more drugs is more likely to get an adverse reaction:

	Number of drugs received by patient	
	without ADR	with ADR
Bergman et al (1971)	4.4	8.0
Hurwitz (1969P)	4.0	9.0
Hoddinott et al (1967)	6.3	12.5

On the average, patients with ADR are found to have received about twice as many drugs as patients without. This is likely to be due to the following four factors:

(a) Since each additional drug given increases the risk of side effect, by simple arithmetic it can be shown that patients with side effects may be expected to have received about a fourth more drugs than patients without side effects.

(b) Patients who are more sick are more likely to receive drugs; and patients who are more sick are more likely to have drug effects. Smith et al (1966): "Patients who received the most drugs and had drug reactions more frequently were more severely ill than patients receiving fewer drugs, according to examination of mortality rates and duration of hospitalization." And Ogilvie and Ruedy (1967) show a very marked rise in ADR rates with severity of illness: Chronic illness, 9.0 per cent; acute illness, 14 per cent; acute exacerbation of chronic illness, 32 per cent.

(c) Patients after an adverse reaction may require another drug. Hurwitz (1969P) notes that an antihistamine was usually given for a rash, and sometimes an antibiotic was changed or new treatment instituted.

(d) Drug interaction may play a part in the small remaining number of cases.

In other words, the impression that drug interaction plays a great part in adverse drug reactions is due to a misunderstanding of the data tabulated above.

(15) Lack of clinical contact: In more detail, Talley and Laventurier (1972I) state, "at this time, no attempt has been made to determine the clinical significance of these potential interactions... It must be emphasized that these potential interactions are reported from computer data totals only and further studies of the individual patient profiles will be needed to evaluate the clinical significance of these identified cases."

(16) Timing: Talley and Laventurier (1972I) programmed their computer to provide information on potentially interacting drugs given within a time frame of 60 days of each other, with one exception (tetracycline-antacid, 6 days). This rigid approach contradicts currently available knowledge. For example, Garb (1971 p. VII) explains: "Some of these interactions occur only when the two drugs are administered within hours of each other... and sometimes the interaction takes place only after one of the drugs has been taken for several weeks." The computer, therefore, should have been adjusted to show different intervals for different drug pairs.

A more conventional approach to this problem was used by Stewart and Cluff (1971); to record interactions in their study, a patient must have been or could have been taking two or more drugs with similar or opposite pharmacologic effects on the same day. And, studying interactions between anticoagulants and other drugs, Kleinman and Griner (1970) recorded potential interactions only if administered for at least 72 hours concurrently with warfarin.

The complexity of timing has been underscored by an experiment on the combined use of chlorpromazine and hexobarbital in mice (Zipf 1965). When one drug was injected 10 minutes before another, the two were antagonistic; when given at the same time, they were synergistic.

(17) Interaction, not incompatibility: Talley and Laventurier (1972D) state that their system checks "for physician-oriented abuses which usually involve poor control of therapy through the prescribing of too many drugs in the same therapeutic category, drugs which interact, or too many drugs for too large a cost." This suggests that they think that drugs which interact should not be prescribed together -- a position at variance with that of all authorities in the field.

As Hansten (1971 p. 1) points out, and as others have pointed out before him, "the terms 'drug incompatibilities' or 'therapeutic incompatibilities' should be avoided. Using the term 'incompatible' implies that two drugs cannot be given concomitantly to one patient. In most cases, however, the interacting drugs may both be given if appropriate precautions such as alterations in dosage, changes in route of administration, or some similar measure are taken."

Provost, Editor of the American Journal of Hospital Pharmacy (1969) states: "It should be borne in mind that all drug interactions are not unintentional or undesirable... superficial information is not enough. Pharmacists must have knowledge of drug interactions in more depth and in better pe spective than many practitioners have demonstrated. A little knowledge can be dangerous."

Finally, Hartshorn (1970), author of the standard Handbook of Drug Interaction, warns that paper work without patient work, as in the study of Talley and Laventurier, is worse than useless:

"The pharmacist, in communicating information about interactions, must have not only available the information, he must also have perspective on the clinical use of the drug, the hazard involved, and a tactful manner in presenting the data. Drug interactions have been called therapeutic incompatibilities. This is exactly the connotation that must be avoided. Drugs which interact are used together -- and often with no problem. The important part is that the physician realize that there is the potential for an interaction and the possible alteration of effect. Very seldom does the situation arise where two drugs cannot be used together. Indiscretion in communication can change the pharmacist from a valuable member of the health team to an 'ignorant pest'."

(18) Scare stories: A current indication of the impact of sensational news stories about adverse drug reactions on therapy is found in the study of Slining and Emmanuel (1973). They noted that 21 per cent of their diabetic patients improperly discontinued their medication as a result of news stories in November 1970, regarding the adverse effect of oral hypoglycemic agents.

Provost (1969) may have foreseen the present situation in an editorial three years ago: "Many pharmacists have seized the subject [of drug interaction] as a drum to beat without acquiring a true appreciation and understanding of the significance or lack of significance of drug interactions in overall drug therapy. In a sense, then, drug interactions, despite the validity of the subject and the legitimate interest in it, has become the profession's latest bandwagon."

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FACT SHEET

Nov. 15, 1972

Of all the national reports and outcries that have been published against the use of Diethylstilbestrol (DES), not one has even mentioned its most potent and unscrupulous use - as a "morning-after pill" administered to women on a national scale, on the suspicion that they may have conceived, without telling them that it is a known potent carcinogen, in lieu of safer but less lucrative methods of post-coital contraception.

The Food and Drug Administration banned DES in cattle feed in minute doses because of clinical evidence that DES in massive doses caused vaginal cancer in 8 women. But the FDA did not ban it for women.

The Natural Resources Defense Council filed a lawsuit charging that DES should be banned from cattle feed because of its carcinogenicity. It made no mention of its routine use on women at many thousand times the dose. Who does the Natural Resources Defense Council defend?

A Nader task force investigated and reported on the carcinogenicity of DES in our food. To our knowledge it did not mention that hundreds of thousands of unsuspecting women are given 11,000 times the dose in the morning-after-pill.[1]

The National Cancer Institute stated at Congressman Fountain's FDA hearings that it "is the better part of reason" to ban chemical carcinogens from food. The NCI did no reasoning at all about banning the same carcinogens from routine "medical" use on women in vastly larger doses.

The National Cancer Institute stated that 2 parts per billion of DES in our daily diet was far too high a dose for such a "spectacular carcinogen". The morning-after pill is 22,000 parts per billion for 5 days, and it is given to women repeatedly. DES is used also as an "anti-miscarriage" drug and is given in daily doses up to 88,000 parts per billion[2] for no other reason than to insure a 'strong healthy pregnancy.'

Cyclamates were banned by the FDA because they caused cancer when fed to mice in massive doses, even though humans take cyclamates in in tiny doses. DES caused cancer in mice (and humans) in tiny doses and it is fed to women in massive doses.

HEW has sought an end to the Tuskegee syphilis study but it has not sought an end to DES studies being done on women years after the first deaths have been reported.

(Note: See Wade, Nicholas, Science, 28 July 1972; Washington Correspondent, Nature, vol. 238, July 14, 1972.)

The Association for the Advancement of Science reported in its Journal Science[3] on the unacceptable uses of DES (at subtraceable levels.) It did not find the use of DES in vast doses on women unacceptable, or even of note. When asked to print this critical information they responded by saying that they "lacked space."[5] Instead they printed a letter condemning "Women's Lib."

Senator Kennedy held subcommittee hearings on the use of DES by farmers to fatten cattle to add to profits. To our knowledge the hearings did not investigate the use of DES as a morning-after-pill, or the continued use of DES in pregnancy.

The National Cancer Institute found the presence of .3 micrograms of DES in a serving of liver intolerable. 200 mg. is given to pregnant women to insure "strong" pregnancies. This is 666,666 times the dose that has been banned by the FDA[4] and that has been condemned by the NCI. Why is the medical profession exempt from the rules that farmers must abide by?

The morning-after pill is a post-coital contraceptive. Many of the women who take it cannot take birth control pills. They are given the morning-after pill precisely for that reason. If they cannot take .5 mg. of synthetic estrogen for 20 days, why are they given 50 mg. of synthetic estrogen for 5 days, repeatedly?

DES is given as an anti-miscarriage drug. The dosage goes progressively from 5 mg. a day at the sixth week of pregnancy to 135 mg. a day by the thirty-fifth week, or even 200 mg. a day.[5] Its estrogenic effects include relaxing the uterine muscle and reducing the possibility of miscarriage or premature births. In 1970 the FDA supposedly sent notices to every physician in the country advising against its usage. Physicians' textbooks still advise its use and pharmaceutical companies still manufacture it to profits of millions of dollars a year. The FDA also endorsed it as "safe" for use as a morning-after-pill at 11,000 times the dose it banned.[6]

DES has resulted in 98 reported cases of vaginal adenocarcinoma in the daughters of pregnant women to whom it was given to insure a "safe" pregnancy and "strong healthy babies."[7] No one knows of the actual number of cases because physicians do not know what they are diagnosing and those who do are not reporting all cases to the National Registry of Clear Cell Adenocarcinoma as they have been instructed to. The reason for this may be that the doctors who diagnose cancer in the daughters are the doctors who administered it to the girls' mothers.[7] Some of the women have already died. (Herbst)

"Thousands, perhaps million of women were administered DES in pregnancy..."[8] Since many university health services in the country are dispensing the morning-after-pill to coeds,[9] we may assume that a large number of these coeds have already been exposed to DES once in utero. No one is notifying these daughters to have the iodine stain test. Instead they are being given more DES. Herbst indicates that it is possible for the massive dose of DES in the morning-after-pill to stimulate the growth of already existent precancerous cells.[9]

We advised one coed who was given the morning-after pill to have the iodine stain test for vaginal cancer, since her mother had been given DES while she carried her. The test was positive and she must undergo operation.[9] It would seem "the better part of reason" for doctors to set themselves to the task of testing millions of daughters for DES-induced cancer rather than socking them with 22,000 parts per billion of DES without so much as inquiring whether they already have precancerous cells from in utero exposure. Physicians know that even natural body estrogen in an infinitesimally small dose can exacerbate the growth of cancer.

Dr. Herbst of Massachusetts General now reports that DES has caused vaginal cancer in offspring at the dosage of just 1½ mg. for just 12 days.[10] The original 98 cases were caused by doses up to 135 mg. for several weeks.

DES caused endometrial cancer in 5 women who had gonadal dysgenesis. One woman had only received 1 mg. of DES for 4 days a week for 5 years.[11] If women want to take in short term massive doses (the morning-after-pill) what has caused cancer in long-term small doses, that is their right. Federal law states, however, that physicians must inform them of the side effects of this drug. Instead coeds have been told DES is "safe and harmless"[12] and worse yet, physicians have been told there are no adverse side effects.[12]

Physicians at the University of Michigan have unilaterally refused to tell the 1,000 women in their study that DES may have cancerous side effects.[12] Physicians at Health Services across the country are doing the same.[12]

DES caused breast cancer in 17 males to whom it was given in treatment of prostate cancer. [13] It was ineffective in treating the prostate cancer and induced cardiovascular disease and blood clotting as a side effect. Breast cancer had hitherto been an extremely rare disease in males.

DES is given to women to keep their hair from falling out for up to 3 months.[14] It is rare indeed for a doctor to inquire of a woman whether she may be pregnant, or to give her a pregnancy test before administering a drug. Pharmacologists report that one side effect of DES is to make hair fall out. Why is DES so enthusiastically endorsed by the medical profession?

DES is given to women, and pregnant women, for acne.

Dr. Anderson of the U. of Michigan Health Service has examined a young man who reports that his mother took DES while she was carrying him. The young man has a third nipple.

DES has produced milk-giving nipples on steers.[15]

DES has caused leukemia and sterility in animals. This evidence helped secure its ban for beef. It did not help get a ban for its use on women.

Evidence began in 1965 that DES causes vaginal cancer in offspring of pregnant women. In 1970 the use of DES on women dramatically increased in the form of the morning-after pill.

Side effects of nausea, vomiting and abdominal cramps with the morning-after pill are so severe that one woman stopped taking the pill before the 5 days were up and remains pregnant,[16] possibly to bear a child who has vaginal cancer. She was not warned of the nausea effects of DES.

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There was no "follow up" done on any of the women who were given the drug who responded to our survey (70 women responded in 2 weeks). They could all have remained pregnant after this dose of DES which is far above the threshhold needed to cause cancer, and the "researcher" would not have known.

"Post-Coital Contraception with Diethylstilbestrol" by Lucille Kuchera, M.D. is the authority by which thousands of physicians began dispensing the morning-after pill. It establishes the abortifacient efficacy of DES at 100%. Yet none of the women who responded to our survey were ever asked if they remained pregnant. We have no way of knowing, nor do they, whether they were part of the "study" or just women who received DES subsequent to it.

None were informed of the known potent carcinogenicity of DES. None were questioned as to whether they experienced severe side effects. Kuchera's article states "no serious side effect was known..." "45.2% had virtualy no side reactions." One respondent told us "I thought I was going to die". One told us she went into a severe diabetic reaction. One reported having to go to the hospital twice the first night for shots of Compazine.

How many doctors know that estrogen can raise or lower blood sugar and is contraindicated in massive doses for diabetic-prone or hypoglycemic-prone patients?[17] Many respondents in our survey reported family histories of diabetes heart disease and cancer. One woman has 4 people in her immediate family with cancer. Blood clots were reported. One with family history/breast cancer has positive Pap Smear since taking the DES. One has a positive test for vaginal cancer or adenocarcinoma.

Synthetic or natural estrogen rapidly increases the growth of existing cancer in the body. It may act as an agent to cause latent cancer to enter its propagation stage. Daughters who had been subjected to DES in utero and had accumulated DES in the uterine and vaginal linings did not experience the growth of adenocarcinoma until they entered puberty and their own estrogen flow began.

Doctors remove the ovaries of thousands of women every year who have breast cancer in an effort to terminate their natural estrogen supply.

It is not known why doctors exhibit such conscientiousness when it comes to the privilege of performing surgery and so little conscientiousness when it comes to conservative and less profitable methods of treatment such as abstention of prescribing DES pills. Doctors who are so anxious to operate to decrease a woman's estrogen supply should desist in giving precancerous women massive synthetic estrogen boosters. Physicians are aware that a woman's family "estrogen profile" serves as an index to her risk of developing some types of cancer. Women with a family history of breast cancer are given the morning-after-pill.[18]

Women who receive the morning-after-pill are not given pregnancy tests to determine if they are carrying a 4-week embryo from a previous intercourse. If the are, the "morning-after pill" will not abort this embryo and that child will grow with the risk of developing vaginal cancer. The morning-after pill is 50 times what is necessary to produce vaginal cancer in offspring.[19]

The FDA supposedly advised doctors in 1970 not to give DES to pregnant women. And yet the FDA advised Dr. Anderson of U. of Michigan Health Service that it was a safe and legal drug when used as a morning-after-pill. The morning-after pill is given to pregnant women. No pregnancy test is used to determine the stage of that pregnancy.

U of M doctors stated to area women that the morning-after-pill was "safe and harmless".[20] They were aware at the time they stated this that Dr. Hertz, Chief of Endocrinology of the National Cancer Institute has stated that results of taking DES may not be detectable for 10 to 20 years.

Dr. Herbst of Massachusetts General reports that adenosis is a condition conducive to contracting adenocarcinoma. He also stated that the endometrial carcinomas produced by DES were identical to the vaginal carcinomas. The uterine lining and the vaginal lining are similar. Estrogen functions to overturn these linings periodically. A massive dose of synthetic estrogen could possibly interfere with this mechanism, causing the aberrant growth of cells. Women were not asked if they had family histories of adenosis or endometriosis which are conducive to lining cancer.[22]

The mechanism of action of the morning-after pill appears to be that it causes some change in the uterine lining, preventing implantation.[23]

Nearly every doctor at the University of Michigan wants DES out of his meat at subtraceable levels. Not one doctor at the University of Michigan has come out against serving DES up to women in massive doses. Not one doctor at the University of Michigan has supported even telling women what is in the morning-after-pill. Are these not the same men who are all for "truth in packaging?"

STUDIES

U of M was able to get 1,000 women to participate in their study, not telling them DES was carcinogenic.

Chicago-Lying-In Hospital was able to get 840 women to participate in a DES-in-pregnancy study by telling them it would give them strong healthy babies. They were given cancer-ridden offspring.

U. of M was able to get nursing students to participate in another (present) study of the effects of synthetic estrogen and progesterone on the pituitary gland by paying them $100. They must sign contracts absolving the doctor of any responsibility. They are in effect being lied to about the possibility of synthetic estrogens causing cancer. Probably they are not being asked about a family history of cancer. Nearly every American family has some cancer in it.

Every woman who registered at the Chicago-Lying-In Hospital between 1950 and 1952 was automatically entered into a study. Half were given DES for the duration of her pregnancy and the lucky ones were given placebos. Women given DES had known liver, kidney, asthma or cardiac problems, diseases where stilboestrol is contraindicated. The study was conducted in an effort to "refute the findings" of a previous study which had involved 632 women at the Free Hospital for Women, Brookline, Mass. along with the help of 117 obstetricians in 18 cities.

Dr. McCartney of the Chicago Lying-In Hospital commented that he is glad for the study because it "provides a basis for studying the long range effect of use of the drug in pregnancy. It would help us a great deal if the patients in the study could be traced." McCartney clearly views cancers in women as helpful data for his profession. Now that women have cancer, if only they will report in, researchers can be enlightened more.

Doctors treated women who had bleeding from vaginal cancer with birth control pills. (More synthetic estrogen to aggravate their cancerous conditions.)

In 1958 a study was conducted on ways to reduce the mortality rate among premature babies. Infants were given different combinations of antibiotics. 45 deaths resulted in those babies that received the antibiotic chloramphenicol. All of the infants came from poor families. "I am proud of that study" states Dr. Joan Hodgman, one of the physicians who conducted it. It was known 7 years before the study began that chloramphenical had severe toxic effects on blood cell-producing tissues.[24]

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It has been known since 1965 that DES causes vaginal cancer. New studies on its contraceptive effectiveness were started in 1969. How many deaths resulted? It takes 10 to 20 years for the effects of DES to become known.[25]

Newsweek and other media have stated to the public that the morning-after pill has "never been known to cause cancer." The morning-after pill is 100% DES. DES has been known to cause cancer. No explanation of a 20-year lag was thought necessary. Women continue to believe doctors who continue to believe the popular media.

None of the doctors at U of M who were involved in the wholesale administration of DES to women were aware of journal articles proving its carcinogenicity.[26]

Hospitals and medical facilities must cease all experimental testing of women with synthetic estrogens on an involuntary basis.

Hospitals and medical facilities must cease all experimental testing of women with synthetic estrogens on a "voluntary" basis. The Tuskegee study was conducted on a "voluntary" or "informed" basis.[27] The New England Journal of Medicine, Sep. 28, 1972 suggests that all exogenous estrogens may play a carcinogenic role.

Research which was undertaken, as that involving the administration of DES to 840 pregnant women, and 636 pregnant women, to refute the findings of a competitor or to duplicate the findings of a colleague must be investigated by the FDA and AMA and damages awarded to experimentees whether harm occurred or not, if they were not informed of the possible or remote side effects of the drugs given them.

Researchers must provide lifetime free treatment for all people diseased from medical experiments.

It will cost every daughter of the "thousands, perhaps millions of women" (Herbst) $120 per year for the rest of her life to be tested.[28] Iodine stain tests of the vaginal walls must be performed in addition to Pap smears. The iodine stains all cells but the cancerous or precancerous cells. It costs $53 for the first test and $30 or $35 dollars every 3 months thereafter. Hearings must be held and a bill must be put through congress insuring that people not be expected to pay the personal and financial costs of abortive medical experiments or involuntary use of fad drugs as DES from 1945 to 1965 was.

Women who were given DES during the fad years as an anti-miscarriage drug were not given a choice of whether to take the drug or not, judging from interviews conducted by Advocates for Medical Information.[29] Statements in medical textbooks illustrate the degree of autonomy given to the doctor and the ignorance on the part of the pregnant woman of the generic medicine she is given by prescription, or even whether it is a medicine, as opposed to a vitamin preparation.

Physicians Desk Reference of 1971 states: "Because of possible adverse reaction on the fetus, the risk of estrogen therapy should be weighed against the possible benefits when diethylstilbestrol is considered for use in known pregnancy." This information is for the doctor, passed on with the patient's prescription at the doctor's "discretion". Why are women never warned directly? Probably because that would give women the autonomy to stop taking a drug without her doctor's permission, something that neither doctors nor drug companies are about to encourage.[30]

Irresponsibility and sadism on the part of medical researchers is evident in the Journal of the AMA Dec. '71. In response to being asked whether an effort would be made to trace the women who had been part of the involuntary study, the AMA Department of Drugs stated: "An organized effort by the medical profession to inform all women who were given estrogen therapy... of the possible tragic consequences for the female offspring is of questionable advisability....a determination of risk must await the results of statistics from reports of hospitals, physicians and tumor registries." The people don't have a right to know when they're being given a drug, and they don't have a right to know when a cancer can be arrested in its early stages.

Cancer Journal 1970 states that women with adenocarcinoma of the vagina have only a 33% survival rate 5 years after radical surgery.

The New England Journal of Medicine, August 17, states "There should no longer be doubt that synthetic estrogens are absolutely contraindicated in pregnancy." (Even when "weighed against the possible benefits"? PDR 71)

Australian Drug Evaluation Committee stated on Sep. 9, 1972 in the Medical Journal of Australia: "stilbestrol should be avoided as a post-coital contraceptive..." Australia banned DES from Australian beef 12 years ago. In this country the FDA permits its use in beef and the AMA permits its use in drugs, liberally. (Vol. 15, No. 40)

Women who request tests for vaginal cancer must be given them, instead of being told they are worrying too much or imagining things because of the press-reports. Paternalism and the "no need to worry" doctrine all too often mean that the doctor does not know how to perform the iodine stain test or has never heard of it.

Women who report adverse side effects from other synthetic estrogens such as the birth control pill must not be referred to psychiatrists by medical doctors. Women who are bleeding from vaginal cancer must not be given birth control pills.

CONCLUSION

The morning-after pill is given to women who have had intercourse on the previous evening even if they were not near their fertile period. Probably about 50% of the women who take it have not even conceived.[31]

Menstrual extraction could be performed on those women who do not come around to their period 2 weeks later and have reason to believe they have conceived. To our knowledge doctors have made no effort to inform women of this alternative. Perhaps this is because it is more time-consuming for doctors and less lucrative for drug companies. It is much easier to push a prescription across a desk.

Every woman who was given DES during pregnancy in the "fad" years must be traced by her obstetrician for the purposes of having her daughters tested. If General Motors can be made to recall a million automobiles because of faults in them, doctors can be made to trace women for the purpose of having drug-induced cancers arrested early.

Demographers estimate that nearly half of all fertilizations result in unsuccessful pregnancies.[32] Miscarriage and spontaneous abortion have been regulating mechanisms for human populations since the beginning of time. Spontaneous abortion and premature birth are as "normal" statistically as carrying a baby to term. Yet doctors give DES to pregnant women to insure against the slightest possibility of miscarriage. This is what the Physicians Desk Reference 1971 refers to as the "beneficial side effects" of carcinogenic DES. Doctors must not decide for a woman whether or not to risk a normal pregnancy. Physicians must be less eager for chemical and moral control over the routine occurrences of pregnancy, as miscarriage always has been.

If the Food and Drug Administration were less protective of the profits of large drug companies,[33] and the medical professionals were less eager to do competitive research, we might assume that neither would want to repeat the tragic mistake of the 1940's and 1950's with a new DES drug, the morning-after pill.

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FOOTNOTES

[1] 50 mg. a day, even when taken with as much as 5 lbs. of food (a generous estimate of a woman's daily intake) represents a DES level of .05 grams per 2270 grams of food. This is equal to 22,000 parts per billion. 2 parts per billion were banned in cattle feed.

[2] 200 mg. a day equals 88,000 parts per billion.

[3] Oct. 2, 1972 Correspondence addressed to K. N. Weiss. *Science* issue Oct. 6, 1972

[4] .3 micrograms of DES are present in 1 lb liver. A woman who takes 200 mg. DES with 1 lb. of food gets 666,666 times .3 micrograms.

[5] Dr. Herbst, Massachusetts General Hospital and the National Registry of Clear Cell Adenocarcinoma reported to Joe Graedon of Advocates for Medical Information Nov. 21 that investigations have shows doctors in some cases to be giving up to 200 mg.

[6] Dr. Anderson of the U. of Michigan Health Service phoned the FDA in Joe Graedon's presence and was assured that since DES is a legal drug, it must be a safe drug.

Physicians textbooks: *Goodman & Gilman Pharmacology Handbook*. *PDR* 1971 *Maternity Nursing*. 1th Ed. Fitzpatrick, Eastman, Reeder. Lippincott: Philadelphia 1966 (nursing school text of U. of M.)

[7] Chicago 1950 study. Reported by Pam Kalishman. *Survival*. Off Our Backs Oct. 1972

Ellen Glovinsky and cousins. Detroit Nov. 1972. See affadavits.

[8] Herbst. JAMA May 1, 1972 Vol. 220 No. 5 Medical News.

[9] Kuchera, Lucille. "Postcoital Contraception with Diethylstilbestrol" from JAMA Oct. 25, 1971 Vol. 218. Copyright 1971 AMA. No statement of carcinogenicity is evident in this article which is used as the authority for the popularization of the morning-after-pill. There is no evidence that coeds anywhere are warned of its carcinogenicity since Kuchera believes and has publicly stated there is none. (Weiss)

Ellen Glovinsky. See affadavits.

[10] Reported by phone to Joe Graedon, pharmacologist of Advocates for Medical Information on Nov. 21. Will be published in Journal of Obstetrics and Gynecology Vol. 40 P. 287 and other places. (Herbst)

[11] Same as above. Also: Only previous reported case of endometrial cancer in patient with gonadal dysgenesis was in patient 79 yrs. old. These cases were in young women.

[12] Statement by Lucille Kuchera, M.D. researcher of the morning-after-pill and Dr. Anderson of U. of M Health Service to press (Michigan Daily Sep.29, 1972

"Post-Coital Contraception with Diethylstilbestrol" Lucille Kuchera, M.D.

[13] Washington Post. David Hawkins. Oct. 29, 1971 Natural Resources Defense Council.

[14] Marcia Federbush. See affadavits. Textbooks and PDR.

[15] Prevention. J. Kinderlehrer. Oct. 1972 P. 121

[16] Kuchera, Lucille. Personal correspondence with Lois Eitzen, reporter for the Michigan Daily. Oct. 1972

[17] Dr. M. G. Yang, Department of Human Nutrition, Michigan State U. Taken from press reports.

[18] See affadavits. Also: Dr. Philip Cole, Harvard Dept. of Epidemiology re "estrogen profile" and inherited cancer tendencies.

[19] Adenocarcinoma produced in offspring with 1 ½ mg. DES for 12 days.

[20] Michigan Daily Sep. 29, 1972 and Oct. 12, 1972

22 See affadavits.

[23] Kuchera, Lucille. "Post Coital Contraception with Diethylstilbestrol" op.cit.

[24] reported by AP News Service Oct. 12, 1972.

[25] Hertz, Chief of Endocrinology, National Cancer Institute

[26] Contact Advocates for Medical Information, Ann Arbor, Mich.

[27] Detroit Free Press, D. Katz, Medical Science writer Nov. 12, 1972

[28] Statement by U. of Michigan Hospital to Advocates for Medical Information

[29] Hallie Stracken. Advocates for Medical Information. See "Cancer and the Morning-After Pill by Kay Weiss. Herself Newsmagazine, Sep. 1972 and other sources.

[30] Suggestion of Ellen Frankford, Vaginal Politics. New York: 1972 Quadrangle

[31] Estimates of Demographers, U. of Michigan. Also: tissue examinations of menstrual extraction, which is done when a woman does not reach her period and has serious reason to believe she is pregnant, shows only 50 % to 85% of those having extraction were actually pregnant.

[32] U. of Michigan. Dept. of Genetics Also: Population Studies. Barrett. Vol. 24, 1970

[33] Nicholas Wade. Science Sep. 28 Vol. 177 No. 4046

We are not interested in banning DES.
We are not interested in banning the morning-after pill.

This report concerns the issue of human experimentation. It concerns the fact that people are not told of the side effects of experimental drugs.

Harrison Welford has informed us that a press report will be released in early December as a result of our data and findings on this problem.

We have uncovered, investigated and researched the use of DES as a post-coital contraceptive. Dr. Herbst and the other authorities mentioned here in connec- ith vaginal cancer + the anti-miscarriage drug had not been aware of it.

HEALTH RESEARCH GROUP
2000 P STREET, N. W.
WASHINGTON, D. C. 20036
872-0320

December 8, 1972

Robben W. Fleming, President
University of Michigan
Ann Arbor, Michigan 48104

Dear President Fleming:

The enclosed report shows that the University has a problem of reckless practice of medicine by health service doctors on female student patients.

The health service is dispensing diethyl stilbestrol (DES) as a postcoital contraceptive, the "Morning-After Pill", a use which does not have Food and Drug Administration approval. DES has not been proven safe and effective for this use. There is strong evidence that DES causes cancer.

A survey by Advocates for Medical Information, an Ann Arbor group (see enclosed report), has shown that health service doctors dispense this pill without informing patients adequately of the long-term risks. Doctors have issued the drug without determining the family and individual history of estrogen exposure and genital or breast cancer, and even without attempt to determine whether the patient is already pregnant from a prior intercourse. Most of the women surveyed received no follow-up of any kind after the drug was prescribed, not even to determine if it had prevented pregnancy.

The desire of health service doctors to meet student needs for prevention of unwanted births is commendable. However, DES is an untested method involving heavy risks. It should be dispensed to students only with the utmost in professional caution, and with full disclosure to the patient of the costs and benefits so that she may balance them herself.

We strongly urge you to place controls on the use of unapproved drugs at the health service. Experiments on students should be conducted only with the close supervision of an institutional review committee. Detailed records should be kept on all such experiments, and all subjects should be completely informed. Doctors who do not know the scientific literature on the drug, should not be allowed to prescribe it.

However dangerous is an experimental drug situation for the patient, the dangers are even greater when novel prescriptions are made outside of controlled experiments, such as occurs at your health service.

A great University cannot allow doctors to practice dangerous medicine on its students, however good the intentions all around.

Sincerely yours,

Anita Johnson

Anita Johnson, esq.

Sidney M. Wolfe M.D.

Sidney M. Wolfe, M.D.

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JAMA
THE JOURNAL of the
American Medical Association
September 20, 1971 Vol 217, No 12

Covert Drug Abuse Among Voluntary Hospitalized Psychiatric Patients

Arnold G. Blumberg, MD; Melvin Cohen, PhD; Audre M. Heaton; and Donald F. Klein, MD

A survey of 332 young psychiatric patients, by means of repeated urinary chromatographic analyses, revealed that at least 60% of these patients employed abusable drugs while hospitalized. Barbiturates were detected most frequently, and addiction did not occur among patients who remained in the hospital. The high incidence of drug abuse in hospitalized patients must be considered in the light of alterations of psychiatric states and in the interpretation of treatment results. The chromatographic screening of the urine of hospitalized patients for nonprescribed drugs is recommended.

Altered behavior in psychiatric patients may be induced by covert drug ingestion with resulting diagnostic and therapeutic confusion. For the purpose of this discussion, we define detectable drug abuse as the self-initiated administration of psychoactive drugs such as amphetamines, barbiturates, tranquilizers, and narcotics for which we have adequate urine-testing methods.

Robinson and Wolkind[1] reported that 16 out of 54 patients (30%) in a psychiatric hospital were shown to have nonprescribed amphetamines in their urine as determined by gas chromatographic techniques. Hekimian and Gershon[2] noted a history of heavy drug use 48 hours prior to admission in 5% of total psychiatric admissions to Bellevue Hospital. Bakewell and Wikler[3] estimated that 6.8% of admissions to a university psychiatric ward were physically dependent on sedatives.

This is an initial report on the incidence of certain types of covert detectable drug abuse among young patients in an open-ward psychiatric hospital over a period of 24 months. We assessed covert drug abuse by means of routine analysis of morning urine collected at regular intervals, ostensibly for kidney-function tests. This communication will present the simple facts of detectable covert drug abuse. More detailed analyses will be reported in future communications concerning psychiatric diagnosis, previous history of drug abuse, hospital course, discharge condition, and follow-up of these patients.

Method

A total of 332 patients were studied. These represented 344 consecutive admissions of patients between 15 and 25 years of age to Hillside Hospital, a 200-bed open-ward voluntary psychiatric hospital. Twelve patients were eliminated from the study because they left the hospital in less than one week or failed to submit a urine specimen while in the hospital. Sixty percent of the study group had a history of drug abuse prior to admission. Patients' covert drug use was followed by serial urine analyses for from 1 to 72 weeks, with an average of 27 weeks. The patients were allowed to go out on pass when their psychiatric condition warranted it, and there was free contact between patients. While selling or distributing abusable drugs was strictly forbidden and in every case where this was discovered the distributor was discharged from the hospital, it is known that illicit drug traffic did occur intramurally.

The urine analytic data were kept completely secret from all other members of the staff, and at no time were the patients or staff aware that the urine samples were being monitored for abusable drugs. A urine sample was requested before admission and at the time of admission on every patient. Under the guise of a statistical survey of urinary creatinine, urine samples were collected every Monday morning since it was thought that the highest incidence of drug abuse would take place over the weekends. The efficacy of urine collection was 84%. Those nurses involved in the supervision of the program were in daily contact with patients and staff and were reasonably certain that there was no significant awareness of the nature of

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From the departments of medical services and research, Hillside Hospital, Glen Oaks, NY.
Reprint requests to P. O. Box 38, Glen Oaks, NY 11004 (Dr. Blumberg).

Table 1.—Incidence of Positive Urine Findings Indicating Covert Drug Abuse

	Drugs		
Incidence	Barbiturates	Amphetamines	Narcotics
1	68	56	34
2	36	13	7
3	27	5	0
4	10	2	0
5	13	3	1
6	9	0	0
7	2	1	0
>7	11	0	0
Totals	176	80	42

Table 2.—Relationship of Admission Urine Findings to In-Hospital Covert Drug Abuse

	Admission Urine	
In Hospital Urine	No Evidence of Drug	Positive Evidence
No evidence of drug abuse	88	22
Positive evidence	97	64
Totals	185	86

the project by anyone in the hospital except the actual personnel responsible for the tests and the medical director.

Analyses were performed by the method of Heaton and Blumberg.[4] The term "narcotic" was used to include morphine, heroin, codeine, cocaine, meperidine, methadone, and propoxyphene. The basis of this method is the thin-layer chromatography of an ether extraction of the urine for barbiturates and the use of ion exchange resin-loaded paper[5] for the extraction of narcotics and amphetamines. By this procedure, a single dose of 100 mg of secobarbital may be detected in the urine up to five days after its ingestion. Amphetamines cannot be found after 48 hours and narcotics cannot be detected more than 36 hours after a single dose. Thus the accuracy of barbiturate determination is almost three times as great as for other drugs, and accordingly, our comparative findings do not necessarily reflect the actual comparative incidence of drug abuse. So as to preserve the conditions of the study, no action was taken in any case where drug abuse was noted. All reported positive urine samples were checked against the nurse's medication records and, where the drug had been prescribed in the course of treatment, the positive findings were not counted.

Results

Table 1 shows the incidence of positive urine findings in 332 psychiatric patients entered in the study. One hundred and ninety-nine patients (60.0%) showed evidence of some drug abuse while in the hospital. One hundred and seventy-six patients (53.0%) showed evidence of covert barbiturate use at least once; 80 patients (24.1%) had positive tests for amphetamines at least once; and 42 patients (12.6%) were found to have a positive test for narcotics at least once. No patient was found to abuse narcotics more than five times and no patient was found to abuse amphetamines more than seven times. The heaviest barbiturate use was found in a patient who had 16 positive samples in 25 studied over a period of 44 weeks. Of the 42 narcotics users, 38 used barbiturates and amphetamines as well. Forty-six patients abused both amphetamines and barbiturates, and the remainder used barbititurates or amphetamines only. The choice of narcotic drugs broke down as follows: meperidine, 7 patients; morphine and heroin, 20 patients; codeine, 13 patients; cocaine, 5 patients; and propoxyphene, 6 patients.

Since the use of drugs appears episodic rather than continuous, repeated testing is necessary if offenders are to be detected. Moreover, patients leaving the hospital early have fewer tests and thus there is less opportunity for detection of drug abuse. The chance of finding at least a single positive test for drug abuse rises sharply with increased testing up to ten tests, and then continues to increase gradually. Of the 236 patients who had ten tests or more, 166 showed a positive test for drug abuse.

Urine samples were obtained prior to or at the time of admission from 271 of the 332 patients studied. Of these, 86 showed evidence of the presence of abusable drugs. The relationship of positive urine findings prior to hospital control to the subsequent finding of drug abuse in the course of hospitalization is shown in Table 2.

A positive urine on admission is significant as a predictor of subsequent drug abuse, as is indicated here by a Chi square equal to 10.64, df = 1, $P < 0.01$. If the group under study is limited only to patients who were in the hospital long enough to have at least ten urine samples studied, the prognostic value of the admission urine is somewhat more striking. Thus, while 74% of all patients with positive urine samples on admission subsequently showed positive evidence of drug abuse in the hospital, 87% of these patients showed subsequent covert drug abuse while in the hospital if at least ten urines were tested.

Comment

A majority of the young patients in an open-ward psychiatric hospital were noted to have evidence of detectable drug abuse while hospitalized. The overwhelming preponderance of this use was occasional rather than constant. Barbiturates were found more than twice as often as amphetamines and almost four times more often than narcotics. This apparent preference may be spurious, reflecting the persistent detectability of barbiturates in the urine for much longer periods than other drugs.

Despite the presence of drug abuse on an occasional basis, the finding of persistent drug abuse was extremely rare. The occasional use of narcotics was observed but in no case was associated with addiction. Morphine, in the form of heroin, was most commonly seen, with codeine next in popularity. It is possible that heavily drug-dependent patients left the hospital early and as such are not represented in our population.

Goldstein and Brown[6] have outlined statistical methods for assessing the true incidence of drug abuse from the analyses of randomly collected urine samples. Their calculations cannot be projected to these data since our urine samples were not collected randomly. These authors indicated, however, that statistical analysis with less than ten samples would incur intolerable error. We recommend that any analysis for covert drug use involve at least ten separate urine analyses. If more tests can be done, a still higher incidence of episodic drug abuse will be detected.

Covert drug abuse was eventually demonstrated in 52% of patients whose urine on admission showed no evidence of drug abuse, as compared with 74% of patients whose urine was positive on admission. Thus the presence of a positive urine on admission statistically increases the likelihood of drug abuse in the hospital; but a negative finding on admission should not lead one to discount the possibility of subsequent drug abuse. A high index of suspicion is indicated in all young hospitalized psychiatric patients.

At present, no satisfactory method is available for detecting the use of a number of psychoactive substances such as marijuana, lysergic acid diethylamide (LSD), and glue. Alcohol could be checked by breath analysis or blood analysis. Our estimates of drug abuse based on the methods specified must result in underestimates if all significant drugs were to be considered.

It appears that young voluntary psychiatric patients employ abusable drugs frequently, in apparent disregard of the known treatment policy of the hospital. It is important to take this into consideration in evaluating psychiatric treatment in the presence of apparently inexplicable mood shifts. Psychotropic drugs are often synergistic or antagonistic with abusable drugs. The sedative action of barbiturates is markedly increased by phenothiazines. Hypertensive crises may result when patients on a monoamine oxidase inhibitor take amphetamines. Pharmacological studies in psychiatric hospitals should be controlled by routine urine analyses to take into account the high probability of contamination of data by drug abuse. Lubran[7] has summarized many published reports concerning the effects of barbiturates and narcotics on standard laboratory tests such as prothrombin time, bilirubin, liver microsomal enzymes, sulfobromophthallein (Bromsulphalein) retention, amylase, and lipase. Clinicians must therefore consider the possibility of drug abuse in the evaluation of laboratory reports.

Conclusions

(1) Drug abuse occurs in a majority of a voluntary young psychiatric inpatient population despite reasonable prohibition and control. (2) Drug abuse is usually episodic. Addiction is not observed in the population which remains in a voluntary psychiatric hospital for more than a few weeks. (3) The possibility of drug abuse must be diagnostically considered in the light of possible interaction with prescribed psychotropic medication and in alteration of observed behavior. (4) The possibility of drug abuse must be considered in the evaluation of routine clinical chemistries. (5) Routine, frequently repeated urine analytic procedures for drug abuse are recommended. The value of a urine screening at the time of hospitalization is considered.

This work was supported in part by Public Health Service grant MH 14464 from the National Institute of Mental Health.

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From *Esquire*, March 1969

The Drug Establishment

by James L. Goddard

The makers of prescription drugs are concerned with a very important matter: health (theirs)

An American buying prescription drugs is like no other American at any other counter of any other store in the country. He does not question the high price of the drug; he does not shop around for a cheaper variety; he does not wait for a sale (because there never are any); and he is usually unaware of the name of the drug he is buying, let alone the name of the manufacturer.

Although he is the consumer, he is not the shopper: he buys (on faith) what his doctor has prescribed. He is like a child who goes to the store with his mother's shopping list, which he cannot even read. He is totally unsophisticated as to the workings of the $5,000,000,000 industry to which he is contributing and which his tax money is already helping to support. The consumer of drugs pays up and takes his medicine. And the Drug Establishment, about which he knows nothing, scores again.

The Drug Establishment is a close-knit, self-perpetuating power structure consisting of drug manufacturers, government agencies and select members of the medical profession. There are connecting links between all of the Establishment's flanks, which keep it thriving and well-protected. And a yawning gulf of ignorance separates the whole Establishment from the public at large.

The Drug Establishment savors its detached position, for it creates an ideal climate in which its members can go about their business—making money—while preserving the myth that they are public-spirited saviors of mankind. Drug companies earn an average eighteen percent return on invested capital compared with eight or nine percent for some three dozen other major industries. Nobody questions the great contribution that the drug companies have made to the nation's health over the years, but a number of people, myself included, have begun to question the justification for the enormous price tag they place on their products.

For example, very few people are aware that, aside from manufacturing and distribution, the cost of their prescription includes a share of the industry's annual $800,000,000 advertising and promotion bill; a portion of the $430,000,000 that major companies claim to spend on research and development (much of which is of questionable value); the fees of a battalion of high-priced lawyers who work to find loopholes in federal drug regulations; as well as such incidentals as political campaigns, including the unsuccessful effort (reportedly $95,000 worth) to unseat the Establishment's lonely foe, Senator Gaylord Nelson.

Even fewer people realize that very often they pay for their drugs twice—once at the drugstore and again at tax time. Part of that tax money is used to pay for government-sponsored research (the results of which are often available free to the drug manufacturers) and to buy drugs for use in government health facilities operated by the Armed Services, the Veterans Administration, and the U.S. Public Health Service.

Heading up the Establishment is the Washington-based Pharmaceutical Manufacturers Association, which represents the 135 big money-makers who claim to produce ninety-five percent of the prescription drugs in the marketplace today. Of these 135 companies, fewer than eighty are major corporations: and of these, about thirty-five set the tone for the whole industry. These include such blue-chip companies as Merck & Co.; Chas. Pfizer & Co.; Eli Lilly and Company; Abbott Laboratories; the Schering Corporation; Smith Kline & French Laboratories; Parke, Davis & Co.; The Upjohn Company; G. D. Searle & Co.; and E. R. Squibb & Sons. Operating on an undisclosed, multimillion-dollar budget in dues paid by the companies (who pass the cost on to you) the P.M.A. is able to present a united front to protect the Establishment's business interests against forays by the public, Congress, or any of the federal regulatory agencies.

An offshoot of the P.M.A. is the National Pharmaceutical Council, a splinter group made up of twenty-eight major manufacturers devoted to the maintenance of the brand-name system, which is basic to the aims—and the success—of the Drug Establishment. Mainly a propaganda organization, the N.P.C. issues policy statements on the importance of doctors' prescribing brand-name drugs in order to eliminate any unnecessary risk for themselves. Use of a catchy, easily remembered brand name in journal advertising directly affects the physician's prescribing habits, and obscures the fact that less costly versions may be available under the generic name of the drug.

The second major group within the Establishment is the scientific and medical community. Theoretically, this should include 300,000 physicians, 96,000 dentists, 120,000 pharmacists, 40,000 medical laboratory technologists, and 89,500 health-related research and development professionals. But it doesn't. In fact, there are only a few thousand Establishment figures to be found throughout the professions, with less than a thousand key medical spokesmen, strategically located researchers, and administrators of medicine and research—who spend most of their efforts maintaining the cordial relationships between industry and government.

The third element, strangely enough, is the government, which supports the Establishment by such devices as using taxpayers' money to buy back from the manufacturers drugs that taxpayers' money helped to develop.

Opposing the Establishment we have Senator Gaylord Nelson (D.-Wis.)—and that's about all. Senator Russell B. Long (D.-La.) is also trying to change the system, but his approach (advocating the inclusion of a drug benefit under Medicare) is different, and he has not been carrying on the same kind of one-man war currently being waged in Senator Nelson's Monopoly Subcommittee. For almost two years now, Nelson—flanked by his legislative aide William Cherkasky and subcommittee economist Benjamin Gordon—has been conducting an investigation into the pricing policies of the Drug Establishment. His efforts have produced some useful headlines, but his subcommittee is investigative, not legislative, his resources are limited (Gordon works practically alone), and the dents that his crusading lance has made in the Establishment's armor are relatively small. One of Nelson's greatest problems is that he is championing the cause of a public that doesn't really know how much it needs a champion.

But the Establishment is always concerned when someone takes an interest in its activities. Ranks are closed, the drawbridge is hauled up, and the vast machinery of defense hums smoothly into operation. Press releases pour out of P.M.A.'s Washington headquarters by the thousand, answering, point by point, the testimony of witnesses critical of the industry (often before the witness has completed his testimony). P.M.A.'s erudite president, C. Joseph Stetler, travels the country defending American business against intrusion by "Big Government," as represented by Nelson's "biased" hearings, telling the "real" story of the pharmaceutical industry's contribution to medical care, and how drug prices have actually gone down despite the enormous funds that the companies pour into research and development. And at each session of the hearings, the majority of the public seats in the huge Caucus Room of the Old Senate Office Building are occupied by Establishment lawyers and company representatives.

FAVORABLE DIAGNOSES

The Family Doctor.

American Medical Association

Through its unselective acceptance of P.M.A. ads in its Journal, the A.M.A. keeps the Establishment healthy.

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  (F.D.A., National Academy of Sciences)
Dr. Thomas Hayes
Dr. Harry Shirkey, Vice-Chairman
  (N.Y. Acad. Sci., F.D.A.)

DOCTORS IN RESIDENCE

In relation to drugs, these are among the most important doctors in the country

Alabama
Durris R. Boshell
S. R. Hill, Jr.

California
George M. Akin
Robert C. Batterman
James Y. P. Chen
Eliot Corday
Wilfrid J. Dixon
John D. French
Robert J. Glaser
George C. Griffith
Leo F. Hollister
Chauncey Leake
Sherman M. Mellinkoff
Wilfried F. Mommaerts
William Reeves
Morton K. Rubinstein
Harold J. Simon
Joel Solomon
Reuben Straus

Delaware
Jurg A. Schneider

Hawaii
Harry C. Shirkey

Missouri
Solomon Garb

Nevada
Joseph C. Elia

New Jersey
Carl C. Pfeiffer
Irving I. A. Tabachnick

New York
Clara M. Ambrus
Julian L. Ambrus
Eugene Y. Berger
Steven Carson
Alfred Gilman
Jerome M. Glassman
Norman B. Kanof
John H. Laragh
Gerhard Levy
K. C. Mezey
Bernard L. Oser
Henry I. Russek
Aldo P. Truant

Ohio
Charles W. Denko
Harriet T. Dustan
Edward D. Frohlich
Irvine H. Page

The Professional Societies

At their annual meetings, P.M.A. "detail" men buttonhole doctors. (The first name of each society is "American.")

Society for Pharmacology and Experimental Therapeutics
College of Clinical Pharmacology and Chemotherapy
Association of Clinical Chemists
Academy of Pediatrics
Cancer Society
Association for Cancer Research
College of Obstetricians and Gynecologists
College of Physicians
Academy of General Practice
Society for Clinical Investigation
Society for Experimental Pathology
Society of Tropical Medicine and Hygiene
Association of Immunologists
Federation for Clinical Research
Neurological Association
Psychiatric Association
Rheumatism Society
Heart Association

Congressional Friends

Senate
Hugh Scott (R—Pa.)
Everett M. Dirksen (R—Ill.)
Jacob K. Javits (R—N.Y.)

House
Clarence J. Brown Jr. (R—Ohio)
Florence P. Dwyer (R—N.J.)
John D. Dingell (D—Mich.)
Wilbur D. Mills (D—Ark.)
Paul G. Rogers (D—Fla.)
Dr. Durward G. Hall (R—Mo.)
Dr. Tim Lee Carter (R—Ky.)
Staffer: Gregg Potvin (Dingell)

National Academy of Sciences Drug Research Board

A government advisory group strongly influenced by P.M.A.

Dr. Karl H. Beyer Jr. (Merck)
Dr. Leighton E. Cluff (F.D.A. Consultant)
Dr. Maxwell Finland (Boston City Hospital, Harvard)
Dr. Alfred Gilman (Albert Einstein College of Medicine)
Professional Staff Member: D. C. Trexler

Standard References

Two government publications and two private ones provide varying lists of drugs, but none is sufficient or complete in itself for use by a prescribing doctor.

United States Pharmacopeia
  Gives the chemical descriptions of all prescription drugs
    Lloyd C. Miller
    Dr. John Adriani, Revision Committee
National Formulary
  Describes the chemical actions of drugs, but not usage or effect on patients.
    Edward G. Feldmann
New Drugs, published and sold by A.M.A.
Physicians' Desk Reference
  Published by Medical Economics this one lists primarily P.M.A. Drugs.
    Albert B. Miller, General Manager
    Barbara Huff, Compilation Editor
    Dr. Austin Joiner, Medical Consultant

PEP PILLS

Drug companies spend $800,000,000 a year (or $3000 per American doctor) taking ads, giving out samples, gifts, setting up "award" dinners and golf tournaments to promote their own drugs.

Ad Agencies

L. W. Frohlich & Co. Inc.
Donald F. Fitzsimmons Inc.
William Douglas McAdams Inc.
Sudler & Hennessey Inc.
Dean L. Burdick Associates Inc.
N. W. Ayer & Son Inc.
Ted Gotthelf Associates Ltd.
William Esty Co. Inc.
Robert E. Wilson Inc.
Sullivan, Stauffer, Colwell & Bayles Inc.
The Shaller-Rubin Co. Inc.
Paul Klemtner and Co. Inc.
Robert A. Becker Inc.
Kallir, Philips, Ross Inc.
Lambert and Feasley Inc.

Media

Supported in large measure by drug-industry advertising.

The Journal of the American Medical Association
  (Dr. Austin Smith, former editor)
The New England Journal of Medicine
M.D.
  Dr. Felix Marti Ibanez, Editor
  Dr. Michael Fry, Managing Editor
Medical Tribune
  Dr. John Adriani, Advisory Board Member

Pharmaceutical Manufacturers Association (P.M.A.)

Its purpose is to see that its members, the big makers of brand-name prescription drugs, stay healthy and rich

C. Joseph Stetler, President

Board

E. Claiborne Robins, Chairman A. H. Robins
Richard M. Furlaud, President Squibb Beech-Nut Inc.
Dr. Theodore G. Klumpp, President Winthrop Laboratories
W. H. Conzen, President Schering Corporation
Dr. Austin Smith, President Parke, Davis & Company
F. Gifford Upjohn, Chairman The Upjohn Company
P.M.A. Staff Attorney: Rodney Munsey

Industry Members

They make brand name prescription drugs.

Syntex Laboratories Inc.
Hoffmann-La Roche Inc.
  Dr. Robert I. Robinson
Merck & Co. Inc.
  Dr. Karl H. Beyer Jr.
Chas. Pfizer & Co. Inc.
Eli Lilly and Company
Abbott Laboratories

ANTIBIOTICS

Industry Law Firms

They fight off P.M.A. foes, namely the regulatory agencies such as F.D.A.

Wilmer Cutler & Pickering
  Lloyd Cutler
Covington & Burling
  H. Thomas ("Tommy") Austern, Stanley L. Temko, Richard A. Merrill, Peter Barton Hutt
Kirkland, Ellis, Hodson, Chaffetz and Masters
Arent, Fox, Kintner, Plotkin & Kahn
Kleinfeld and Kaplan
  Vincent A. Kleinfeld
Wald, Harkrader & Rockefeller
Corcoran, Foley, Youngman & Rowe
  Thomas ("Tommy the Cork") Corcoran
Baker & Mackenzie
Leva, Hawes, Symington, Martin and Oppenheimer
Harter, Calhoun and Williams
  [illegible] Williams
Rhyne & Rhyne
  Charles S. Rhyne
Hamel, Morgan, Park & Saunders
Arnold & Porter

THE POX

In Memoriam

Senator Estes Kefauver (1903-1963)
Fallen leader of the Anti-P.M.A. force.

Congressional Foes

They think drug prices are way out of line.

Senate
Gaylord Nelson (D—Wis.)
Russell B. Long (D—La.)
Philip A. Hart (D—Mich.)
Professional Staffers:
  William Cherkasky (Nelson)
  Benjamin Gordon (Nelson)
  Jay Constantine (Long)

House
L. H. Fountain (D—N.C.)
Benjamin S. Rosenthal (D—N.Y.)
Professional Staffers:
  W. Donald Gray (Fountain)
  Dr. Delphis C. Goldberg (Fountain)

THE PLAGUE

Food and Drug Administration

The F.D.A.'s duty is to regulate P.M.A. members and other drug makers, but it is often stymied by their legal antibodies.

Dr. Herbert L. Ley Jr., Commissioner
Dr. B. Harvey Minchew, Acting Director Bureau of Medicine
  (Dr. Robert J. Robinson, former Director)
  (Dr. Joseph Sadusk, former Acting Director)
Dr. Edwin I. Goldenthal, Office of New Drugs
Dr. John Nestor, Division of Medical Advertising
Dr. John Jennings, Office of Marketed Drugs
General Counsel William W. Goodrich

Federal Trade Commission

The F.T.C. regulates nonprescription-drug advertising and marketing.

Paul Rand Dixon, Chairman
  (former aide to Sen. Estes Kefauver)

Illinois
N. Kenneth Furlong
Rodney P. Gwinn
Louis N. Katz
Max S. Sadove
James G. Armstrong
K. K. Chen
Stanley M. Chernish
Richard S. Griffith
Charles M. Gruber

Louisiana
John Adriani
George Gordon McHardy

Maryland
Charles C. Carpenter
Albert A. Kurland
Arnold M. Seligman
Paul Talalay
Thomas B. Turner

Massachusetts
Leo Alexander
Sidney Farber
Dale G. Friend
Thomas C. Hall
Conan Kornetsky
Maurice Segal

Michigan
Robert D. Laird
Charles F. Weiss
Chris J. D. Zarafonetis

Oklahoma
Stewart Wolf

Pennsylvania
Donald Berkowitz
Joseph R. DiPalma
Jerome A. Gold
George Maha
A. Scriabine

Texas
Joseph W. Goldzieher
Theodore H. Greiner

Virginia
L. W. Hazleton
C. Ross Hart
Albert Wasserman, Jr.

Washington, D.C.
F. Paul Alepa
Edward D. Freis
Christopher M. Martin

Wisconsin
Richard I. H. Wang

BOOSTER SHOT

Uncle Sam buys $500,000,000 worth of drugs each year with taxpayers' money.

Government Purchasers
Defense Supply Agency
(Department of Defense)
Veterans Administration
Robert A. Statler, Director of Pharmacy Services
U.S. Public Health Service

THE DONORS

200,000 000 Americans. They buy five billion dollars' worth of drugs each year and give the Drug Establishment an additional billion-dollar transfusion in taxes appropriated for drug research and government purchases of drugs.

Medical World News
Dr. Morris Fishbein, Editor
Modern Medicine
Clinical Pharmacology and Therapeutics
Dr. Walter Modell, Editor
Dr. Karl H. Beyer Jr., Editorial Board Member
U.S. Medicine
Robert J. Benford (former public-relations staffer for P.M.A.)

WET NURSES

With $580,000 000 in public funds, these agencies oversee government research of drugs, make findings available free to P.M.A. members.

Labor, H. E. W. and Related Agencies Subcommittees of the Senate and House Appropriations Committees
Almost half of the funds appropriated by this committee for government drug research goes to institutes within the states its members represent.

Sen. Jacob K. Javits (R—N.Y.)
Sen. Clifford P. Case (R—N.J.)
Sen. Warren Magnuson (D—Wash.)
Rep. Daniel J. Flood (D—Pa.)
Rep. Melvin R. Laird (R—Wis.)
Rep. Robert H. Michel (R—Ill.)

Department of Health, Education, and Welfare
Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs, H.E.W.
U.S. Public Health Service
Dr. William Stewart, Surgeon General
National Institutes of Health
Dr. Robert Q. Marston, Director
Dr. Roderick Murray, Director, Division of Biologics Standards

Research Institutes
Roswell Park Memorial Institute (New York State Department of Health)
University of California
Massachusetts General Hospital
Johns Hopkins University
State University of New York Upstate/Downstate Medical Centers
Stanford University
Sloan-Kettering Institute for Cancer Research
S.R.I.
Arthur D. Little
Palo Alto Medical Research Foundation

Veterans Administration
$43,000,000 budget for drug research
Dr. Thomas C. Chalmers, Asst. Chief Medical Director for Research and Education
Dr. Lionel M. Bornstein, Director of Research Services

Smith Kline & French Laboratories
Schering Corporation
The Upjohn Company
G. D. Searle & Co.
Lederle Laboratories (American Cyanamid Company)
Parke, Davis & Company
Dr. Austin Smith, Pres. (former Pres. P.M.A.)
Dr. Joseph Sadusk, V.-P. for Med. Affairs
E. R. Squibb & Sons Inc.

Proprietary Association
The fraternity of over-the-counter drug manufacturers. More competitive, more open to the public, less "establishment" than P.M.A.

Board
Hermon A. High, President, Senior Vice-President Richardson Merrell Inc.
James D. Cope, Executive Vice President and Treasurer
Dr. Joseph M. Pisani, Vice-President for Medical and Scientific Affairs
W. H. Conzen, President Schering Corporation
Dr. J. Mark Hiebert, Chairman of the Board Sterling Drug Inc.
William F. Laporte, Chairman of the Board and President American Home Products Corporation
Frank Markoe Jr., Senior Vice-President, Secretary, and General Counsel Warner-Lambert Pharmaceutical Company
H. W. Munroe, Vick International Division of Richardson-Merrell Inc.

Members
American Cyanamid Company
Bristol-Myers Company
Carter Products, Division of Carter-Wallace Inc.
Chesebrough-Pond's Inc.
Toilet Articles Pharmaceutical Division of Colgate Palmolive Company
Ex-Lax Inc.
Johnson & Johnson
Madison Laboratories, Proprietary Division of Ciba Pharmaceutical Company
The Mennen Company
The Mentholatum Company
Miles Laboratories Inc.
Chas. Pfizer & Company Inc.
Lydia E. Pinkham Medical Company
Plough Inc.
Vick Chemical Company
Sterling Drug Inc., Glenbrook Laboratories Division
Sears, Roebuck & Company

Mudge, Rose, Guthrie, Alexander and Mitchell
(Richard Nixon, former partner)

VACCINE
National Pharmaceutical Council
This association of brand-name manufacturers (all are P.M.A. members) guards against contamination of the market by cheaper generic drugs.

Vernon O. Trygstad, President
Joan K. Weston, Vice-President (former Secretary of A.M.A.'s Council on Drugs)
H. Thomas Austern, Stanley L. Temko, and Richard A. Morrill of Covington, Burling: Attorneys

Books
By Prescription Only
Morton Mintz
Handbook of Prescription Drugs
Dr. Richard Burack
The Real Voice
Richard Harris
Medical Messiahs
James Harvey Young
A.M.A., Voice of American Medicine
James G. Burrow
The Medicine Show
Consumers Union
Doctors' Dilemmas
Louis Lasagna
Medicine Makers
N. Walker

TYPHOID MARYS

Generic Companies
Small manufacturers. They sell generic drugs at a fraction of P.M.A. members' brand-name prices. A bad sign. Not yet an epidemic.

Cord Laboratories
American Pharmaceutical Company
Leo Linden Laboratories
Premo Pharmaceutical Laboratories
Purepac Corporation
Bryant Pharmaceutical Corporation
Carrtone Laboratories Inc.
Davis Edwards Pharmacal
S. B. Penick & Company
Hudson Pharmacal Company
Maizel Laboratories Inc.
Majestic Drug Company Inc.
Milan Pharmaceuticals Inc.
North American Pharmacal Inc.
Nysco Laboratories Inc.
Palmedico Inc.
Philadelphia Laboratories Inc.
Southern Drug and Manufacturing Company Inc.
S S T. Corporation
U. S. Ethicals
West-Ward Pharmaceuticals Inc.
Xttrium Labs Inc.

Chief Carrier
Drug Compendium (proposed), a doctors' reference book which would describe cost, usage, dosage, effects and side effects of all existing drugs, listing brand names and generics side-by-side. It would supplant the Physicians' Desk Reference which lists mainly brand-name drugs

Stray Viruses
The Medical Letter
A frank independent newsletter for prescribing doctors.
The New Republic
Never kindly disposed to the Drug Establishment, N.R. has published several highly critical articles.
Consumer Reports
When it deals with drugs, it lists brands and generics side-by-side.

The cost of this defense is passed on to you.

The Food and Drug Administration is not, strictly speaking, an opponent of the Establishment, but it functions rather in the capacity of a public "watchdog." Besides approving drugs for marketing on the basis of their safety and efficacy, F.D.A. also inspects marketed drugs for purity and safety and enforces regulations designed to prevent companies from making false and misleading advertising claims. When regulations are breached, the agency's "ultimate weapon" (short of criminal action, brought through the Department of Justice) is the recall. In cases where a product is found to be impure, the compound can be ordered off the market until the matter is cleared up.

Recalls involving impurity or mislabeling are relatively simple, but advertising is the Establishment's shop window to the physician, and any attempt at "tampering" is met with massive resistance. P.M.A. lawyers descended like locusts on the latest F.D.A. proposal to revise the ad regulations, and arguments—both legal and semantic—flew back and forth for months (at your expense).

Keeping a close eye on the F.D.A. is Representative L. H. Fountain (D.-N.C.), chairman of the Intergovernmental Relations Subcommittee of the House Committee on Government Operations. With the aid of two extremely able investigators, W. Donald Gray and Dr. Delphis C. Goldberg, Representative Fountain's task is to make sure the F.D.A. really does work in the public interest. Like the Nelson subcommittee, however, the Fountain subcommittee's role is purely investigative. It does not possess the same powerful sanctions as the appropriations or legislative committees dealing with health matters. The real source of its power is exposure and coercion through the press and public opinion.

The Drug Establishment functions with all the smoothness of an intricate Swiss watch. To find out how it works, and why your prescription costs so much, let us trace the path of a mythical drug through the expensive maze that leads to your medicine cabinet. We shall call it *blythophrene.* It has an airy, genial, "in" sound—just right for an Establishment model.

Blythophrene may first appear at any one of a number of places within the Establishment. It may be a promising chemical entity discovered in a company basic-research project. In this case there are no problems; the company merely patents the compound, informs the F.D.A. that it is an Investigational New Drug and that they plan to follow certain steps to explore its potential, and they are off and running. In another case, it may be the result of research carried out by an independent investigator who makes a deal with the company for the patent rights. From this point, the company's action is the same as before. In a third instance, blythophrene may be the product of government-sponsored research—

in which case the process becomes a little more complicated.

To begin with, drug companies own the vast majority of screening and testing facilities that are vital to defining the potential uses of promising compounds—which gives them a virtual stranglehold on the development of drugs in this country. Prior to 1962, the companies routinely made tests on drugs developed by government-sponsored investigators in return for certain rights to the development and marketing of promising drugs.

But in 1962 the Department of Health, Education, and Welfare—in a move designed to prevent the exploitation of publicly funded inventions for private gain—changed its patent policy. All inventions involving federal funds were to be reported to the Surgeon General of H.E.W., who would then decide on the disposition of the patent rights.

The new system broke down, however, partly because of administrative difficulties, but more importantly because the Establishment suddenly closed the door to its screening and testing facilities. John Conner, then president of Merck, Sharpe & Dohme and later Secretary of Commerce, told a 1962 meeting at Johns Hopkins University that the companies would refuse to cooperate in producing drugs developed from government research unless the patent policy was changed to allow them to patent the drugs in the latter stages of their development.

The blockade was so effective that in 1967 H.E.W. was forced to back off somewhat and allow the testing company to patent "new" uses of compounds which it may discover at its own expense without the participation of the government investigator, even "where such new use is within the field of research work supported by the grant."

This is an important loophole, because not all the potential uses of a drug can be determined prior to the screening and testing procedure. For example, if early research indicated that blythophrene might have limited use in the treatment of schizophrenia, but the company, through the screening procedure, discovered that it would also be extremely valuable as a tranquilizer, then blythophrene could be patented by the company for that purpose.

P.M.A.'s president, C. Joseph Stetler, hailed the move as "a much needed improvement . . . a progressive measure," and there was a sudden upswing in the number of agreements signed between government grantees and pharmaceutical companies.

Problems still exist, however, particularly with compounds of limited uses. Last year, U.S. Comptroller General Elmer B. Staats was called on to evaluate the usefulness of the $53,000,000 public investment in basic drug research between 1962 and 1967, and found that the loss of industry screening services had seriously limited the usefulness of government-sponsored research. He noted the improvement since the 1967 revision and urged the Secretary of H.E.W. to take further steps to resolve the remaining problems.

The result may be that the government will have to back down further and allow the Establishment to reap even larger profits by selling back to the public the results of research that was paid for primarily with public funds.

But let us assume that blythophrene has been born in a manufacturer's lab. That means it is safe in the hands of the Establishment, which now has to consider its future. There is a long period of research and development ahead before blythophrene can make its contribution to the company's profit margin. To save itself a great deal of money, the company tries to interest one of the federal drug-research programs which, if all goes well, will then undertake to do all the research free for the company at taxpayers' expense.

For the purpose of illustration, blythophrene is a catecholamine —a substance that plays an important role in treatment of psychiatric illness. Psychopharmacology is a fashionable field at the moment, and our compound is of great interest to the National Institute of Mental Health, through which most of the government's contribution to psychopharmacological research funds are channeled.

Blythophrene, therefore, finds its way to the New Senate Office Building, and the mahogany-and-leather-appointed hearing room of the Labor-H.E.W., and Related Agencies Subcommittee of the Senate Committee on Appropriations. Here, until the end of 1968, Senator Lister Hill (D.-Ala.) presided with dignity, charm, and an anecdotal memory.

The records show that proper presentation by government witnesses before the subcommittee will pay off, and blythophrene will be a good bet for inclusion in one of the Institute's important programs. The drug company gets a windfall. But it is not alone.

N.I.M.H. is not the only unit within H.E.W.'s Public Health Service that does drug research. Every one of the eight National Institutes of Health, the Division of Biologics Standards (where vaccines, serums, and derivatives of human blood are approved) and the N.I.H. Clinical Center in Bethesda, Maryland, with four thousand inpatients and three thousand outpatients a year, carry out large-scale drug research with public funds. The Department of Defense, the Veterans Administration, and the Public Health Service also conduct research programs that benefit the Establishment.

It is difficult to establish exactly how much of the $1,400,000,000 annual budget appropriated for N.I.H. is used for drug research, but a good example of the kind of service that your government provides for the Drug Establishment with your money is the National Heart Institute's new Coronary Drug Study.

Heart disease is the nation's major killer, claiming a million lives each year. An important cause of the disease is the high fat content of the American diet. The high fat intake is thought to increase the blood levels of a substance called cholesterol, which gradually forms deposits on the artery walls, reducing the flow of blood and resulting, eventually, in a heart attack.

Four compounds that reduce cholesterol levels in the blood are already on the market, and N.H.I. has designed a project to learn whether they can effectively prevent heart attacks. One of the drugs—nicotinic acid—is widely available, but the other three, Premarin, Clofibrate, and Choloxin, are the exclusive property of two Establishment drug firms.

Premarin and Clofibrate are marketed by Ayerst Laboratories, Division of American Home Products Corporation, and Choloxin by Travenol Laboratories, a division of Baxter Laboratories.

Some fifty-five clinics have already joined the National Heart Institute's project, and some 8500 people will ultimately be enrolled. The estimated total cost is $40,000,000, and the results—if positive—will mean vastly increased sales of those drugs.

The companies' contribution? They merely provide the investigators with free supplies of the drugs.

You may be wondering just what the pharmaceutical manufacturers do with the huge sums they claim to set aside for research and development each year. So did the late Senator Estes Kefauver, who couldn't find out when he conducted his famous hearings in 1961 and 1962, and Senator Nelson has had little more success during the two years of his investigation. Much of the industry's own research has to be secret, of course, but Establishment bookkeeping procedures apparently are so circuitous that some company presidents themselves claim not to be able to provide even a generalized breakdown.

Only the Establishment knows for sure how much of its own research makes a genuine contribution to drug development—and its members aren't telling. The Establishment is aware of the interest, however, and in its annual report for 1967 the P.M.A. made an effort to appease the questioners.

The report said that seventy-eight P.M.A. members—the ones that accomplish most of the industry's research—had budgeted $430,900,000 for "R&D Expenditures for Human-use Drugs" during 1967. It even went so far as to define "R&D Expenditures" as "the total cost incurred for all pharmaceutical and medical research and development activity. These figures include the cost of direct salaries, other direct costs, services, routine supplies, and supporting costs, plus a fair share of overhead (administration, depreciation, space charges, rent, etc.) for pharmaceutical research and development."

The report went on to say that of the $430,900,000 total, $374,100,000 was to be spent inside the firms, and $56,800,000 outside.

Of this latter portion, $16,600,000 goes to other companies, private laboratories, and foreign countries. And since as a rule no pharmaceutical company has, on its own premises or as part of its corporation, a clinic or hospital for the human testing on new drugs, this means that only $40,200,000 is available for this most important purpose. Representing a mere 8.9 percent of the Establishment's "research" investment, this pays for research carried out by private practitioners and consultants, and by investigators in medical schools, hospitals, and clinics.

Now, if we take another Establishment claim—that "industry has invested $7,000,000 in research and development costs for every new and significant drug that has reached the public during the past decade"—we find that the 8.9 percent of it that went into human testing comes to $623,000. Compare that to the N.H.I. project just mentioned in which *you* are spending $10,000,000 on human testing on each of three Establishment drugs. Then remember that if the drugs *do* perform their function, you will have to pay for them all over again at the drugstore.

The disposition of the bulk of the Establishment's R&D expenditures is impossible to determine. We know that some of the research carried out by pharmaceutical companies is both important and valuable—but we don't know how much. In their efforts to find new drugs, the companies collected thousands of soil samples and plants from all over the world and ran them through a complex screening process for any sign of chemical activity that might be turned into a useful drug. This was a long and costly procedure, and sometimes important new compounds were discovered as a result. However, with up to seventy-eight companies doing this screening, much of it had to be duplicative, and, therefore, wasteful.

Testing new compounds in animals is another important contribution made by the pharmaceutical manufacturers, but again, we do not know what proportion of the overall research figure is allocated for this purpose. And, as I shall explain later, some of this is wasteful.

For the rest, we do not know how much is spent on the salaries of men whose job it is to comb the scientific literature for clues on what the competition is up to. Some of these "clues" can lead to another important activity performed by drug-company chemists. It is known as "molecular manipulation," and it is a means of circumventing competitors' patents.

Let us say that Company A has obtained a patent on a compound with an extremely promising future. Company B (and possibly others) spots the compound's chemical formula in the literature and, not wanting to be left out in the cold, sets to work to come up with something similar. Company B chemists take the chemical formula and attempt to change its structure in such a way that it will perform essentially the same function, but at the same time will not infringe Company A's patent rights. In a few cases, this molecular manipulation will result in an improved drug, but for the most part what comes on to the market is just another "me-too" drug that makes no contribution to medical science at all.

Then there is "phony" research, performed purely for advertising and promotional purposes. This particularly involves the animal studies, and I saw many instances of it while I was F.D.A. Commissioner. In these cases, company scientists carry out "testing" on animals, the results of which can be predicted in advance, merely to flesh out the supporting bibliography that the law states must accompany any promotional or advertising literature in which therapeutic claims are made for the drug. On the surface, these "studies" look genuine, but many of them are performed well after other research has defined the uses of the compound under study.

Useful or not, industry research and development is a legitimate business expense and therefore tax deductible. Besides, by the time blythophrene reaches the marketplace, you can be sure it has absorbed its share of these costs.

Before we get blythophrene into the drugstore, however, there is another element that should be mentioned as an illustration of the way in which the Drug Establishment is self-perpetuating. This is the National Academy of Sciences-National Research Council's Drug Research Board, which maintains "broad surveillance of therapeutic research in all its phases and provides a forum in which the interests and responsibilities of investigative medicine, industry, and government may be reconciled."

The Academy was established by Congress in 1863 as an adviser to the federal government on matters concerning science, engineering, and technology. Like its counterparts in other fields within the Academy, the Drug Research Board is available "for advice to agencies of government and to private organizations with responsibilities related to research on drugs," and its opinions carry great weight in the determination of public policy.

The concept of the Board is an admirable one. Around its meeting tables can be gathered together the best thinking in government, industry, and science. The objective is to produce the optimum opinions about drugs for the health of the nation. The Board has certainly dealt with some fundamental issues in the drug area. Nevertheless, when we move from concept to reality, we see that the Board is composed of the same individuals who work elsewhere in the marketplace. The Board represents not only the best of government, industry, and science; it is, by its very membership, a limited forum in which consensus is developed for the Establishment, and in which the consensus prevails. One illustration comes quickly to mind:

While still Commissioner of the F.D.A., I advocated the publication of a national Drug Compendium that would provide, for the nation's physicians, a single source of information (including prices) on all drugs currently on the market. The listing would include important prescribing information, not only for the brand names marketed by the big Establishment companies, but also the cheaper equivalents that are put out by lesser-known non-Establishment manufacturers, of which there are several hundred. There is no such source available to physicians currently, aside from the *Physicians' Desk Reference*, which is published annually by *Medical Economics*. This is far from complete and lists only those drugs whose manufacturers are willing to pay for the inclusion of their products. The companies represented are mainly Establishment companies.

When the Compendium was first discussed with the N.A.S.-N.R.C. Drug Research Board, it met with a degree of acceptance—but not enough to overcome the Establishment's opposition to having its products listed on an equal basis with those of non-Establishment companies. The lack of the Board's unqualified support was a factor in the failure of Congress to act on a bill to establish the Compendium.

In the case of a single drug such as blythophrene, the Board's role is relatively simple. They may be asked, by N.I.H. or the developing company, to evaluate the early research on the compound and provide an assessment of its potential value to medical science. If they decide it has little promise, they will simply say so. If their opinion of blythophrene's potential is high, however, this will be an important factor in the allocation of public funds to blythophrene investigators.

If blythophrene is the product of government research alone, the Board's opinion will arouse the interest of industry in developing a patentable product from the compound.

It's time to get blythophrene to market. And this is where the Establishment comes face to face with the Food and Drug Administration; for, in order to obtain F.D.A. approval, the company that developed the drug must file a New Drug Application that proves that blythophrene is both safe and effective in the treatment of those conditions for which they claim it may be prescribed.

In an effort to impress the F.D.A. with overwhelming evidence that blythophrene should be made available to the public immediately, the company puts together a grab bag containing every scrap of research with human beings that has been done, whether by government researchers, investigators in academic institutions or hospital centers, or industry-supported private physicians who want to do some "research" and who use their private patients as volunteers. Often, as many as forty cartons of "evidence" on a single drug will arrive at the F.D.A.'s Bureau of Medicine. The Bureau is staffed by two hundred physicians, as well as pharmacists and other professional and administrative personnel, whose job it is to sift through this mountain of paper and reach a decision on the drug's future.

Unfortunately, with the emphasis on quantity rather than quality, this is sometimes difficult to do. Time and taxpayers' money are often wasted while the Bureau personnel examine the evidence only to find that important data are missing. The company is then asked to provide the missing information. While Commissioner, I found that too much of the evidence submitted by the companies in support of their New Drug Applications consisted of poorly conceived and badly controlled "clinical studies" that added nothing to the data on the drug's safety and efficacy. I said many times, both publicly and in private discussions with manufacturers, I would prefer to see a few, well-controlled studies, performed by experienced investigators, than hundreds of minor studies, performed on a few patients by private practitioners who are not really suited to that kind of work.

If my suggestion were to be adopted, F.D.A. personnel would be involved in less paper work, they would be provided with all the data necessary to make a speedy, scientific decision—and the drug would reach the public sooner. However, as can be seen by the National Heart Institute's Coronary Drug Project, such studies can be both time-consuming and costly—and the Drug Establishment prefers to leave that kind of risk-taking to the government. At any rate, submissions to F.D.A. based on my suggested concept were very few and far between.

If blythophrene is safe and effective, F.D.A. will approve it for marketing. But while this decision is being made, another battle is being fought on another front. This concerns the wording of the "package insert"—the descriptive material that accompanies each package of blythophrene to the drugstore, outlining the recommended dosages, indications for use, side effects, and contraindications. This, along with the wording of the claims that may be made in advertising material, is also the responsibility of the Food and Drug Administration.

This is extremely important to the pharmaceutical companies, because this is where the money is. They have to convince the physician that this is the best possible product in its field. F.D.A. on the other hand, must make sure that the advertising claims remain within the bounds of scientific evidence.

High-priced lawyers will spend hours in conference with F.D.A. officials, haggling over the wording of promotional material, engaging in semantic arguments as to *(Continued on page 152)*

THE DRUG ESTABLISHMENT

(Continued from page 121) whether a certain section of government regulations does or does not give F.D.A. the right to limit the company's "freedom" in a certain area. Eventually, at your expense, agreement is reached, and the company is ready to launch blythophrene with a gigantic advertising campaign aimed at the physicians who, they hope, will prescribe the drug freely.

The Drug Establishment's advertising campaigns are among the most impressive in all media. The advertising and promotional budget has been estimated at approximately $800,000,000 per year—or about $3-000 for each physician in the U.S.

The campaigns embrace not only professional journal advertisements (the *Journal of the American Medical Association* leads the field with an income hitting close to $10,500,000 per year), but also convention exhibits, seminars, workshops, closed-circuit television, FM radio, motion pictures, slide shows, golf tournaments, dinners, annual awards, and "detailing." (The detail man is a personal salesman who goes from doctor's office to doctor's office, spending an average of six minutes extolling the virtues of his company's newest or most trusted product, disparaging competitive products, leaving behind free samples, calendars, pens, and other memorabilia.) One company traditionally hands out to every new medical-school graduate a brand-new stethoscope for his very own.

With large sums at their disposal, the advertising agencies that handle pharmaceuticals are among the elite of the advertising and promotion business. Among the most prominent are L. W. Frohlich & Company, who has handled Parke, Davis & Company for years; Donald F. Fitzsimmons, Inc.; William Douglas McAdams, Inc., who shares offices with *Medical Tribune* and *Hospital Tribune*; Sudler & Hennessey, Inc.; Paul Klemtner & Company, Inc.; William Esty Company, Inc.; and Robert E. Wilson, Inc. Except for Fitzsimmons and Esty, all are associate members of the Pharmaceutical Manufacturers Association.

Liberally sprinkled with drug ads that often run to eight four-color pages, the various professional and semiprofessional journals have been willing carriers of the message of the Drug Establishment. Naturally, they find it hard to agree with almost anything said by federal regulatory agencies. This is understandable. The Establishment holds together very well at this point. For example, Dr. John Adriani, chairman of the A.M.A.'s Council on Drugs and one-time adviser to the F.D.A., is a good friend of Dr. Arthur Sackler, eminent New York psychiatrist and former chairman of the board of the William Douglas McAdams advertising agency. Dr. Adriani serves on the Editorial Advisory Board of *Medical Tribune*. Dr. Morris Fishbein, former A.M.A. president and editor of its *Journal*, is editor of *Medical World News*, McGraw-Hill's leader in "mass-circulation" news magazines aimed at physicians and second in advertising revenue.

The Establishment's powerful grip on the physician's reading material is important, not only as a means of putting across its own sales pitch, but also because very often it is the only source of drug information that the doctor has. By assaulting his eyes with thousands of colorful "brand-name" ads, the Establishment can blind him to the fact that, in many instances, cheaper versions of the same drug are available from lesser-known manufacturers.

Establishment propaganda holds that only those drugs produced by "research-oriented, quality-conscious" drug companies can be said to be safe and effective. Anything else—particularly anything made by the smaller, non-Establishment companies—is potentially dangerous.

The facts speak differently, however, because all drugs, whether sold under brand names or generic names, have to meet certain chemical standards set by two national agencies, the U.S. Pharmacopeia and the National Formulary. These standards cannot guarantee equivalency, but they do ensure that the drugs are pure and potent.

In addition, the cheaper "generics" appear to be good enough to pass the rigorous tests laid down by federal agencies, such as the Department of Defense, which form the major part of the smaller firms' market, buying large quantities of drugs on a bid basis. The small companies, with lower production and distribution costs and no advertising or research overhead, often outbid the Establishment firms for such contracts.

There are exceptions, and the F.D.A. is spending additional tax dollars on research to find out whether the costly brand-name products really are better than their cheaper counterparts. But on the basis of the available evidence it can reasonably be said that two drugs, which contain the same active ingredients and meet the same chemical standards required before marketing approval can be given, will act the same way in the human body.

However, when I tried to list brand-name drugs and their so-called "generic equivalents" together in our proposed Drug Compendium, the Drug Research Board balked at the idea. Their opinion—which coincided with the Drug Establishment's view—is that the generic drugs have yet to be proved as good as brand names.

The lengths to which Establishment figures will go to protect the myth of brand-name superiority is perhaps best illustrated by Senator Nelson's confrontation with W. H. Conzen, president of Schering Corporation.

Nelson was particularly interested in the pricing structure of Meticorten, Schering's brand of prednisone, an important anti-inflammatory agent used in the treatment of chronic arthritis, allergies, and skin and eye inflammation. Many versions of the drug are available, and the prices range from Schering's $170 per thousand to $4.53 per thousand for a version manufactured by Upjohn. Many non-Establishment companies have prednisone available in the Upjohn price range.

Mr. Conzen was asked whether the Defense Supply Agency—"which is supplying Walter Reed, where Presidents, Congressmen, and generals are treated"—was getting an inferior product when it accepted the lower-priced prednisone.

"I cannot say whether it is therapeutically equivalent," Mr. Conzen said. "I can say that they are definitely buying a first-class drug which complies with and meets the tests and standards of the agency, which are very exact."

Yes, but "what is there about Meticorten that makes it worth $170 a thousand, when the government is buying it for $4.53 [and] New York City is buying it for $4.58 a thousand?" Senator Nelson asked.

"Several points," Mr. Conzen said. "One, the overwhelming clinical evidence as to the efficacy of our brand unmatched by any other brand or make of prednisone. Second, our continuing research and the contributions which the sale of Meticorten make to enable us to continue to compete in this business as a research-oriented company, which strives for innovation, and plays its part in bringing benefits to the public, which, in terms of health and anything else, are unsurpassed anywhere in the world."

Mr. Conzen, also in his testimony, spoke of Schering's discovery of prednisone in 1954 and the research that his company puts into new drugs of that kind. Actually, between 1953 and 1967, the National Institutes of Health invested a total of $16,498,144 in grants for research on prednisone and its cousin prednisolone. (With annual sales of $1,000,000, one-third of the total U.S. prednisone market, it is unlikely Schering's investment in research is near this figure.)

The government-sponsored research really paid off for Schering. Shortly before the drug was approved for marketing, the results of an important study carried out at the N.I.H. Clinical Center were reported to a meeting of the American Rheumatism Society. This assured the immediate success of Meticorten. The prestige of the National Institutes of Health was put behind the drug; physicians responded by making it the leading seller in the field.

The stock market also responded, and Schering's stock rose from $11 per share to $80.

Mr. Conzen was merely following the Establishment line, memorized and repeated by all Establishment figures when confronted with bothersome questions concerning the high cost of their drugs. Harold Burrows, former president of Parke, Davis & Co., told Senator Nelson: "Our sales policy has to be such as, hopefully, to produce an economic climate in which we will be inspired and encouraged to spend money for research, if the health and well-being of this country and of the world is to be advanced. I think that the ethical pharmaceutical industry, including Parke, Davis, has made a significant contribution in that field and we hope to continue to do so."

The climate is healthy enough; no one will dispute that. Annual reports for 1967 for just a few Establishment companies reveal the state of the industry's health: Merck & Co. had sales of $528,000,000, a net profit of $89,000,000 on an investment of 25.4 percent; Smith Kline & French had sales of $260,000,000, a net profit of $42,000,000 and a return of 26.9 percent; Eli Lilly & Co. had sales of $408,000,000, a net profit of $54,000,000, and a return of 19.2 percent; and G. D. Searle had sales of $133,000,000, a net profit of $27,000,000, and a return of 28.5 percent.

The question arises, therefore: With the nation irrevocably committed to providing broader and better health care for all its citizens, and committed as well to build drugs into that guaranteed health-care system, is it reasonable for this small group of companies to charge prices that return such extravagant profits—especially when the public investment is overwhelming at the beginning (during the research and development stage) and at the end (at the time of purchase for defense and civilian medical-care programs)?

I think that the answer should be No. But the Establishment is firmly entrenched, supported by an unknowing public and a captive medical profession. Until there is strong, organized opposition, the Drug Establishment is safe.

This lack of organization is the major reason for the failure of opponents of the Establishment to make any real headway. Too often we find the various branches of government, which should be looking out for the public interest, fighting among themselves.

There are many examples, but the worst that I can recall during my term as Commissioner involved a dispute between the F.D.A. and Senator Edward V. Long (D.-Mo.). Senator Long, champion of the right to privacy, assigned a staff consultant, Miles Hadley Robinson, M.D., to investigate the F.D.A. Between March and October, 1967, Robinson—quite properly while he was a Senate employee—made several thousand copies of secret F.D.A. documents—with particular emphasis on those concerning a drug called Cothyrobal, submitted for approval by the Vascular Pharmaceutical Co.

Robinson resigned from Long's staff on April 12, 1968. Four days later he appeared at F.D.A. with Louis Mishell, both representing Vascular Pharmaceutical, and requested "a fair decision by F.D.A. on the Cothyrobal application"—meaning approval for marketing.

This was one of the most open examples of conflict of interest that I had ever known, and while Robinson's investigation was going on, Senator Long was making speeches harshly critical of the F.D.A., in the Senate, to the press, and in his home state.

The F.D.A. survived, and Senator Long was retired by the Missouri voters, but this kind of dangerous and unnecessary backbiting is typical of the problems that must be overcome if we are to counterbalance the enormous power of the Drug Establishment. If you undermine the public's confidence in its "watchdog," you destroy your main weapon.

The public investment in development of drugs is too large to permit the continuation of a system under which a few companies are allowed to make huge profits at public expense. As we move closer to our aim for quality health care for all Americans, public attention will focus more and more on the Drug Establishment and they will see the need for change. Drugs are a vital health commodity and they must be freely available to all who need them—not just those who can afford them.

The necessary changes could be made within the present system, if the Establishment were willing to cooperate reasonably and rationally. By trimming advertising costs, eliminating unnecessary research, and cooperating, rather than competing, with the government in the development of new drugs, the pharmaceutical industry could deliver drugs to the public at much lower prices—and still make a reasonable profit.

If the Establishment insists on following its present course, however, an awakened public will have no alternative but to demand a system of governmental control.

Under the American system, the likelihood of nationalization is remote—but it is conceivable that as the public investment in the health industry grows larger, the Drug Establishment may well find itself in the position of explaining to Congress why it should not be made into a public utility. ###

Senator **Kennedy.** Tomorrow we will look into behavior research, psychosurgery, electrical stimulation of the brain.

The hearings will begin at 10 a.m., in room 4232.

[Whereupon, at 12:25 p.m., the hearing was adjourned to reconvene at 10 a.m., February 23, 1973.]

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